

Poliovirus Containment Advisory Group (CAG)

CAG2
November 2017
Meeting report

**Report of the Second Meeting of the
Containment Advisory Group (CAG)**

Hotel Intercontinental, Geneva
28 – 30 November 2017

CONTENTS

SUMMARY RECORD OF RECOMMENDATIONS	3
NOTE FOR THE RECORD	7
Introduction.....	7
Background	7
Participants	7
Context, objectives and expected outcomes of the meeting.....	7
Updates	8
CAG discussions, conclusions and recommendations	9
Issue 1: Novel strains/CAG-Expert Support Group (ESG)	9
Issue 2: New technologies for vaccine production.....	10
Issue 3: Environmental surveillance	10
Issue 4: Secondary safeguards	11
Issue 5: Tertiary safeguards.....	12
Issue 6: Phase I for PV1 and PV3	13
Issue 7: Activities allowed in PV-non-essential facilities post-eradication.....	14
Issue 8: Genetic stability tests	14
Issue 9: Storage outside of containment.....	15
Issue 10: RNA.....	16
Issue 11: Guidance for the establishment of NACs	18
Issue 12: Documented records.....	18
Issue 13: Immunization of facility personnel: maintaining mucosal immunity in facility operators post-OPV cessation.....	19
Issue 14: Post-exposure protocol	20
Issue 15: The shower.....	21
Issue 16: Dedicated facilities, work on campaign basis.....	23
Issue 17: Dedicated air supply.....	24
Issue 18: Ventilation system and backflow protection/prevention	25
Issue 19: Effluent decontamination	26
Issue 20: Dedicated effluent treatment plant	27
Issue 21: Guidance for non-poliovirus facilities	28
Issue 22: TRS 926.....	29
Other issues discussed at the 2nd CAG meeting	30
Responsibilities for GAPIII-related decisions	30
Communicating GAPIII changes	30
Date of next meeting	30
Annex 1: Abbreviations	31

SUMMARY RECORD OF RECOMMENDATIONS

The Containment Advisory Group (CAG) held its second meeting on 28 - 30 November 2017 in Geneva, Switzerland.

1. Novel strains/CAG-ESG

In order for CAG to determine the containment requirements for novel Sabin strains, the CAG-ESG needs to look at available data on genetic stability, reversion, behaviour in the environment and in-vivo human studies, and determine what additional data are required. Based on these, the CAG will make a position statement.

CP applications should address work with novel strains. NACs and the GCC-CWG may ask CAG for guidance before issuing certificates.

2. New technologies for vaccine production

CP applications should address work with new technologies. NACs and the GCC-CWG may ask CAG for guidance before their decision on such applications.

3. Environmental surveillance

The CAG did not recommend any changes to the GAPIII section titled "*Rationale*", but welcomed the fact that WHO is drafting the document *Public Health Management of a Breach of Type 2 Poliovirus Containment* where the issue of environmental surveillance will be addressed in the context of a containment breach or some other event of concern (e.g. history of issues) that would trigger wider environmental surveillance.

4. Secondary safeguards

The CAG secretariat will request the SAGE, through its SAGE Polio Working Group, to clarify, based on SAGE's recent recommendations, the requirements for IPV doses, population immunity, vaccine coverage, and geographical challenges.

Until a decision is made by SAGE, issues around secondary safeguards in CP applications submitted to NACs/CWG may be referred to CAG for guidance.

5. Tertiary safeguards

Delete Subelement 12.3.1 (b) in the following instances:

Annex 2 under "*Requirements for Containment of WPV2*";

Annex 3 under "*Requirements for Containment of OPV2/Sabin2 PV materials*"; and

Annex 3 under "*Requirements for Final Containment of all OPV/Sabin PV materials*".

Subelement 12.3.1 (b) remains unchanged in Annex 2 under "*Final containment of all WPV*":

Poliovirus facilities are located in areas with demonstrated low poliovirus reproductive rates (R_0), i.e. in areas with closed sewage systems with secondary or greater treatment of effluents.

In other terms, recommendations listed under Issue 5 and Issue 19 in this report clarify that:

Facilities handling 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, but do not need to be located in areas demonstrating closed sewage systems with secondary or greater treatment of effluents.

6. Phase I for PV1 and PV3

The CAG recommends countries, through their National Certification Committees, to start the inventory, destruction or preparation for containment of PV1 and PV3 as soon as the new *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses* is published.

The CAG endorses the GCC's recommendation for RCCs to announce the request for countries (NCCs) to complete the inventory, destruction or preparation for containment of WPV1 and WPV3 as soon as possible and no later than the end of Phase II.

7. **Activities allowed in PV-non-essential facilities post-eradication**

This issue was postponed for discussion at a later meeting. The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

8. **Genetic stability tests**

This issue was postponed for discussion at a later meeting. The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

9. **Storage outside of containment**

Modify the recommendation made at the 1st CAG Meeting as follows (new text in **bold**):

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) for an interim certificate of containment (ICC) **as well as for a certificate of containment (CC)** assessment. Any derogations applied for and accepted by the NAC will be reflected on the certificate scope and associated certificates, **and regularly reassessed.**

10. **RNA**

The CAG reorganized for clarity the definition developed at the 1st CAG meeting, as follows (reorganized/new text in **bold**):

Poliovirus nucleic acid: ~~Nucleic acid that has been extracted/purified using methods demonstrated to inactivate poliovirus~~ **Poliovirus 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) using methods demonstrated to inactivate poliovirus, or synthesized RNA or cDNA (e.g., cDNA clone, synthetic transcript).** Poliovirus nucleic acid 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 in the "**Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses**") 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).~~*

11. **Guidance for the establishment of NACs**

This issue was postponed for discussion at a later meeting. The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

12. **Documented records**

Modify Subelement 1.4.2 (as updated at the 1st CAG meeting) as follows (new text in **bold**):

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 and **are** available for review during **containment** certification **audits.***

If not already in place, the collection and retention of records, documents and data should start immediately.

13. Immunization of facility personnel: maintaining mucosal immunity in facility operators post-OPV cessation

This issue was postponed for discussion at a later meeting. The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

14. Post-exposure protocol

The NAC should demonstrate that there are effective linkages between the response and contingency plans addressing containment breaches in place at the facility and at national level.

15. The shower

The GAPIII requirements in Subelement 12.3.1 (g) of Annexes 2 and 3, as modified at the 1st CAG meeting, were not changed.

The CAG assigned a subgroup to the task to review the issue of mandatory showering, consider the information and evidence around the need/benefits of shower-out (including adherence to the precautionary principle to minimize the risk of release of poliovirus post eradication to as close as possible to zero), and evaluate whether or not a robust set of criteria could be developed for use in risk assessments to justify the omission of routine showering-out. The CAG agreed to discuss this issue by teleconference in January 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

16. Dedicated facilities, work on campaign basis

Subelement 12.3.1 (c), of Annexes 2 and 3 was not changed.

17. Dedicated air supply

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

18. Ventilation system and backflow protection/prevention

The CAG recommended to modify Subelement 12.3.1 (i) in Annex 2 (under "Requirements for Final Containment of all WPV") as follows (new text in **bold**):

*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 **passing across the polio containment boundary (liquids, gases)** and via measures to prevent release through traps, sinks and shower drains.*

19. Effluent decontamination

The CAG recommended to modify Subelement 12.3.1 (i) in Annex 2 (under "Requirements for Containment of WPV2") and in Annex 3 as follows (new text in **bold**):

~~*Throughout the Poliovirus type 2 containment period, a dose of IPV will be introduced, high global vaccine coverage will be maintained (population immunity is not expected to decline) and the use of mOPV2 for outbreak response is considered. Where evidence of satisfactory implementation of primary and secondary safeguards (described in GAPIII) is provided, the decontamination of effluents is not required.*~~

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 passing across the polio containment boundary (liquids, gases) and via measures to prevent release through traps, sinks and shower drains.

In other terms, this recommendation clarifies that:

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.

20. Dedicated effluent treatment plant

The CAG recommended to modify the line on effluent treatment and its associated Footnote 3 in Table 1 as follows:

~~Dedicated~~ Effluent treatment plant: ~~No~~-Not dedicated³ / ~~No~~-Not dedicated³ / **Yes** Dedicated⁴

Footnote 3: ~~Untreated release into a closed sewage system with secondary effluent treatment in the facility location (all~~ **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}.

21. Guidance for non-poliovirus facilities

The CAG adopted the *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*, subject to amendments in a final round of comments to be provided by CAG members within a week of the 2nd CAG meeting. The CAG recommended that the guidance be published and distributed to relevant national authorities as soon as possible.

22. TRS 926 Annex 2

The CAG welcomed the revision of TRS 926 Annex 2 to align it with GAPIII, committed to providing its consolidated comments as soon as possible, and planned to discuss this issue further at a CAG teleconference in January 2018.

NOTE FOR THE RECORD

Introduction

Background

The Containment Advisory Group (CAG), nominated in March 2017 and formally constituted in November 2017, is an advisory body to the Director-General of WHO. Its role is to make recommendations on technical issues related to the implementation of the Global Plan of Action for Poliovirus Containment (GAPIII)¹. 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 Second Meeting of the CAG was held on 28–30 November 2017 at the Hotel Intercontinental in Geneva, Switzerland.

Participants

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

Additional participants included Dr Paul Huntly (WHO expert biorisk management consultant), and Dr Steve Oberste and Dr Bruce Thorley of the drafting group of the *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*.

Dr Arlene King of the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC), also representing the GCC Containment Working Group (GCC-CWG), participated as an observer.

Context, objectives and expected outcomes of the meeting

An open call for submission² of technical issues linked to GAPIII was published on the Global Polio Eradication Initiative website from 21 August to 1 October 2017 in preparation for the 2nd CAG meeting. The secretariat received 22 submissions in response to this call, as well as two draft guidelines^{3, 4} submitted for review by the CAG. The orange booklet with all submissions was shared electronically with the CAG members two weeks ahead of the meeting, and the guidance documents one week ahead of the meeting. In addition, 7 issues from the 1st CAG Meeting were tabled for discussion at the 2nd CAG meeting.

The 2nd CAG meeting had the following objectives:

1. Provide GAPIII orientation to CAG members before technical issues related to GAPIII are discussed;

¹ Available at: http://polioeradication.org/wp-content/uploads/2016/12/GAPIII_2014.pdf

² Available at: <http://polioeradication.org/wp-content/uploads/2016/10/RequestCAG2Nov2017.docx>

³ *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*. Draft for CAG, 20 November 2017.

⁴ Revision of WHO Technical Report Series (TRS) 926, Annex 2. *Guidelines for the safe production and quality control of poliomyelitis vaccine*. 2nd draft version 6 November 2017.

2. Resume discussions on priority issues for which CAG requested at its meeting of June 2017 that feedback be collected from other stakeholder groups first;
3. Discuss issues submitted to CAG for consideration;
4. Discuss the *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for poliovirus* in view of its endorsement and publication.

Updates

Dr Roland Sutter updated the CAG on progress with polio eradication. WPV type 1 continues to be widespread in Pakistan and Afghanistan, and outbreaks of VDPV2 have been reported from the Democratic Republic of the Congo and Syria. The risk of international spread of poliovirus remains a Public Health Emergency of International Concern under the International Health Regulations. Following the withdrawal of OPV2, 35 countries still do not use IPV routinely. To mitigate the impact of supply shortages the WHO Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the use of fractional doses of IPV. Transition planning for surveillance and long term containment of polio is among the 7 organizational risks identified for WHO. Funding from GPEI is decreasing. For some countries this funding constitutes more than 40% of their total polio budgets. Resources must be found to maintain global surveillance, containment and access to needed vaccines.

Dr Sutter then outlined the way forward in containment and eradication of poliovirus. He described the structures and responsibilities of actors engaged in polio eradication, the main stakeholders and the possible incentives and deterrents that could promote compliance with GAPIII requirements. He gave an overview of progress made in developing new, safer viral strains and technologies for the production of poliomyelitis vaccines, and emphasized that polio eradication is a long term endeavour that needs flexible planning if it is to succeed.

Dr Arlene King and Mr Neil Godden reported back from the GCC meeting held on 23-25 October 2017. The GCC is responsible to oversee Objective 3 of the Global Polio Eradication Strategy, "Contain poliovirus and certify interruption of transmission". As part of this role the GCC countersigns certificates issued in line with CCS by the national authorities for containment (NACs) to polio-essential facilities (PEFs). In the discussion, CAG members emphasized the importance of clear communication with stakeholders, the important role of the NACs as the authorities that will enforce poliovirus containment in countries, and the need for sustainable resourcing of GCC/CWG and NACs to enable timely review of applications and containment certification audits to uniform and clear standards.

CAG discussions, conclusions and recommendations

Dr Paul Huntly provided an orientation to the relevant sections of GAPIII before each issue was discussed.

Issue 1: Novel strains/CAG-Expert Support Group (ESG)

Relevant GAPIII section

Introduction (last paragraph):

(...) *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.*

History

Summary of request submitted to the 1st CAG Meeting ("CAG1")

Clarify the containment requirements for novel poliovirus strains.

CAG1 recommendation

Create a CAG Expert Support Group (CAG-ESG members identified at the 1st CAG meeting include Dr Mark Pallansch, Professor George Griffin, Dr Stephen MacAdam) to consider containment requirements for novel poliovirus strains and propose potential solutions to the CAG and other groups if necessary, for review and approval.

Summary of issues raised

Some genetically modified, more attenuated novel Sabin strains are being developed in view of their use as surrogates for current Sabin strains, including for IPV production. These novel strains may represent a major advantage if the containment requirements for their handling and storage can be agreed to be lower than the ones that apply for Sabin strains.

Summary of requests to CAG

CAG was asked to determine containment requirements for the handling and storage of novel poliovirus strains.

Summary of CAG discussions and conclusions

The CAG considered that available data on genetic stability and attenuation of the available novel strains are not sufficient to exclude the risk of replication, transmission, and loss of attenuation in humans.

CAG recommendation

In order for CAG to determine the containment requirements for novel Sabin strains, the CAG-ESG needs to look at available data on genetic stability, reversion, behaviour in the environment and in-vivo human studies, and determine what additional data are required. Based on these, the CAG will make a position statement.

CP applications should address work with novel strains. NACs and the GCC-CWG may ask CAG for guidance before issuing certificates.

Way forward

WHO will ensure that the CAG-ESG addresses the issue of novel Sabin strains and submits their position to CAG for consideration and discussion at one of the upcoming CAG teleconferences planned in Q1 2018. Novel poliovirus strains and nOPV (see issue 2 below) are planned to be discussed during the same teleconference. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 2: New technologies for vaccine production

Relevant GAPIII sections

(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.

and

Introduction (last paragraph):

(...) 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.

History

Summary of requests to CAG1

Encourage low risk poliovirus vaccine manufacturing techniques, including the development of virus-like particles (VLPs).

CAG1 recommendation

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.

Summary of CAG discussions and conclusions

The CAG was informed that clinical trials with nOPV took place in containment in Belgium in summer 2017. Data are being collected, and data analysis is planned to be conducted in January/February 2018. These data will then be presented to the CAG-ESG and CAG for consideration. The CAG-ESG will review the data and present their findings, including requests for additional data, to the CAG at the second planned CAG teleconference in Q1 2018.

CAG recommendation

CP applications should address work with new technologies. NACs and the GCC-CWG may ask CAG for guidance before their decision on such applications.

Way forward

The issue of new technologies for vaccine production will be addressed at one of the upcoming CAG teleconferences planned in Q1 2018. By then more information will have become available to CAG-ESG for review, as a basis for providing technical recommendations to CAG for the development of a position statement. nOPV and novel poliovirus strains (see issue 1 above) are planned to be discussed during the same teleconference in Q1 of 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 3: Environmental surveillance

Relevant GAPIII section

Rationale (fourth paragraph)

The risk from a poliovirus reintroduction can be minimized by locating poliovirus-essential facilities in areas with high levels of population immunity, effective acute flaccid paralysis (AFP) and environmental surveillance, supplemented by efficient public health and response capacity.

Summary of issues raised

The requirement for environmental surveillance at the location of PEFs appears only in the first part of GAPIII, in the chapter Rationale. GAPIII does not say whether and for how long this requirement shall be maintained.

Summary of requests to CAG

State how environmental surveillance should be instituted and for how long it should be maintained.

Summary of CAG discussions and conclusions

The CAG considered that the requirement mentioned in the GAPIII Rationale refers to downstream monitoring of effluents from the facility to detect containment breaches. Wider environmental surveillance should be triggered if a containment breach is suspected. An effective link is needed between the facility's response and contingency plan for containment breaches and the authority responsible for public health surveillance and response. It was noted that the need to establish such a formal link is addressed in the draft WHO *Public Health Management of a Breach of Type 2 Poliovirus Containment* guidance text being developed in the context of the implementation of the International Health Regulations (IHR).

CAG recommendation

The CAG did not recommend any changes to the GAPIII section titled "*Rationale*", but welcomed the fact that WHO is drafting the document *Public Health Management of a Breach of Type 2 Poliovirus Containment* where the issue of environmental surveillance will be addressed in the context of a containment breach or some other event of concern (e.g. history of issues) that would trigger wider environmental surveillance.

Issue 4: Secondary safeguards

Relevant GAPIII sections

(Annexes 2 and 3)

12.3. Infrastructure and Operational Management

12.3.1 Facilities, equipment and processes are designed and run in a safe and secure way with respect to biorisk management. The poliovirus facility shall incorporate features that are guided by assessment of the risk of poliovirus reintroduction to the community and include the following provisions:

a. Poliovirus facilities are located in countries with demonstrated high national immunization coverage (=DTP3 coverage);

and

Strategy, Table 1: GAPIII containment safeguards at a glance

	Poliovirus type 2 containment period	Final poliovirus containment period	
	All type 2 polioviruses	All OPV/Sabin polioviruses	All wild polioviruses
2° safeguards: Population immunity in country hosting the facility			
IPV doses	≥ 1	≥ 1	≥ 3
IPV coverage	= DTP3 coverage ⁵	= DTP3 coverage	>90% ⁶

Summary of issues raised

a. Immunization coverage rates could vary in different areas of a country.

⁵ Diphtheria–tetanus–pertussis vaccine third dose (DTP3) immunization coverage (19).

⁶ Global Vaccine Action Plan 2011–2020 (20).

- b. The number of doses and the administration strategy recommended by the Strategic Advisory Group of Experts on Immunization (SAGE) at its meeting of April 2017 is not consistent with those described in Table 1 of GAPIII.

Summary of requests to CAG

- Allow a subnational (area-based) compliance approach with regard to immunization coverage.
- Update the requirements on IPV doses in Table 1 to be consistent with SAGE recommendations.

Summary of CAG discussions and conclusions

The CAG considered that the SAGE Polio Workgroup is better placed than the CAG to address requirements related to secondary safeguards.

CAG recommendations

The CAG secretariat will request the SAGE, through its SAGE Polio Working Group, to clarify, based on its recent recommendations⁷, the requirements for IPV doses, population immunity, vaccine coverage, and geographical challenges.

Until a decision is made by SAGE, issues around secondary safeguards in CP applications submitted to NACs/CWG may be referred to CAG for guidance.

Follow on action

The specific questions raised on this issue will be brought to the SAGE Polio working group meeting in February 2018, ahead of the SAGE meeting on 17–19 April 2018.

Issue 5: Tertiary safeguards

Relevant GAPIII sections

Annexes 2 and 3, Subelement 12.3.1 (b)

Poliovirus facilities are located in areas with closed sewage systems with secondary or greater treatment of effluents.

and

Strategy - Table 1

	Poliovirus type 2 containment period	Final poliovirus containment period	
	All type 2 polioviruses	All OPV/Sabin polioviruses	All wild polioviruses
3° safeguards: Environment & location			
Siting of facilities in areas with low transmission potential (R_0) for wild polioviruses	No	No	Yes

Summary of issues raised

According to Table 1, PEFs should be allowed to handle and store poliovirus Sabin strains without closed sewage systems at the PEF location. Subelement 12.3.1 (b) in Annexes 2 and 3 of GAPIII is not consistent with Table 1.

Summary of requests to CAG

Delete Subelement 12.3.1 (b) in Annexes 2 and 3 of GAPIII, except in Annex 2 under “*Final containment of all WPV*”.

⁷ Meeting of the Strategic Advisory Group of Experts on immunization, April 2017 – conclusions and Recommendations. Weekly Epidemiological Record No 22, 2017, 92, 301–320. Available at: <http://apps.who.int/iris/bitstream/10665/255611/1/WER9222.pdf?ua=1>

Summary of CAG discussions and conclusions

The CAG agreed to the request and ensure consistency throughout the GAPIII document.

CAG recommendations

Delete Subelement 12.3.1 (b) in the following instances:

Annex 2 under “Requirements for Containment of WPV2”;

Annex 3 under “Requirements for Containment of OPV2/Sabin2 PV materials”;

Annex 3 under “Requirements for Final Containment of all OPV/Sabin PV materials”.

Subelement 12.3.1 (b) remains unchanged in Annex 2 under “Final containment of all WPV”:
Poliovirus facilities are located in areas with demonstrated low poliovirus reproductive rates (R_0), i.e. in areas with closed sewage systems with secondary or greater treatment of effluents.

In other terms, recommendations listed under Issue 5 and Issue 19 in this report clarify that:

Facilities handling 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, but do not need to be located in areas demonstrating closed sewage systems with secondary or greater treatment of effluents.

Issue 6: Phase I for PV1 and PV3

Relevant GAPIII section

Overview of phases

History

Summary of issues raised

GAPIII does not specify Phase I activities in preparation for containment of poliovirus types 1 (PV1) and 3 (PV3).

Summary of requests to CAG1

Consider the inclusion of a Phase I for PV1 and PV3.

CAG1 Meeting recommendations

The CAG secretariat should ensure that GCC discusses and clarifies the timing to start and complete Phase I activities for PV1 and PV3.

Summary of CAG discussions and conclusions

The CAG was informed that the GCC addressed this issue at its meeting on poliovirus containment, held on 23–25 October 2017. The GCC recommended that the Regional Certification Commissions (RCCs) should announce the request for countries to complete Phase I for WPV1 and WPV3 by the end of Phase II, the poliovirus type 2 containment period.

The CAG advised that inventories and destruction or appropriate containment of WPV1 and WPV3 should be completed at end of the containment phase for PV2. Therefore RCCs should call for this to start as soon as possible. This call should be issued in connection with the implementation of the new guidance for non-poliovirus facilities as soon as it is published.

CAG recommendation

The CAG recommends countries, through their National Certification Committees, to start the inventory, destruction or preparation for containment of PV1 and PV3 as soon as the new *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses* is published.

The CAG endorses the GCC’s recommendation for RCCs to announce the request for countries (NCCs) to complete the inventory, destruction or preparation for containment of WPV1 and WPV3 as soon as possible and no later than the end of Phase II.

Issue 7: Activities allowed in PV-non-essential facilities post-eradication

Relevant GAPIII section

Phase implementation

History

Summary of issues raised

GAPIII 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 CAG1

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

CAG1 recommendation

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

Summary of CAG discussions and conclusions

This issue was postponed for discussion at a later meeting.

Way forward

The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 8: Genetic stability tests

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

History

Summary of 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.

CAG1 recommendation

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.

Summary of CAG discussions and conclusions

This issue was postponed for discussion at a later meeting.

Way forward

The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 9: Storage outside of containment

Relevant GAPIII section

Phase implementation

As of the beginning of Phase IIa:

- *The handling and storage of WPV2 material are no longer permitted in poliovirus-non-essential facilities.*
- *(...)*
- *(...) Facilities that have not yet received formal national certification in the containment of poliovirus type 2 are no longer allowed to handle and store WPV2 materials.*

(...)

As of the beginning of Phase IIb (within 3 months of the switch):

- *The handling and storage of OPV2/Sabin2 poliovirus material are no longer permitted in poliovirus-non-essential facilities.*
- *(...)*
- *(...) Facilities that have not yet received formal national certification in the containment of OPV2/Sabin2 poliovirus material are no longer allowed to handle and store OPV2/Sabin2 poliovirus materials.*

The storage of mOPV2 stockpiles (frozen bulk and finished product, prepared in accordance with international requirements 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.

History

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.

CAG1 recommendation

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) 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.

Summary of issues raised

- a. Storage of polioviruses under approved containment conditions that do not meet all GAPIII requirements is only allowed for the period covered by an interim certificate of containment (ICC).
- b. The current draft revision of TRS 926 Annex 2 proposes to allow storage of viral seeds outside the containment area in leak-proof primary containment containers, with specific measures addressing security and access control, inventory, and emergency power source freezer monitoring systems. Two submissions were received requesting clarification on whether viral seed stocks can be stored outside of containment with suitable risk control measures based on a documented risk assessment. This appears inconsistent with GAPIII requirements.
- c. NACs can derogate GAPIII requirements for storage-only facilities. Are risk- and evidence-based derogations (approved by the NAC) allowed for lower risk activities and areas within PEFs handling (not only storing) poliovirus materials?

Summary of requests to CAG

- a. Allow storage of polioviruses under appropriate containment conditions that do not meet all GAPIII requirements for the period covered by the Certificate of Containment (for certified facilities), applying the principles of risk management.

- b. Clarify the GAPIII storage requirements for viral seeds in relation to the requirements in the draft Annex 2 of TRS 926.
- c. Clarify the possibility of using risk- and evidence-based derogations for lower risk activities and areas within PEFs handling/storing poliovirus materials.

Summary of CAG discussions and conclusions

- a. The CAG reaffirmed that the intent of GAPIII is to achieve segregation in storage of live poliovirus-containing materials at facilities. At its 1st meeting the CAG agreed that in granting an ICC, the NAC can accept derogations for specific requirements identified by the PEF that would not contribute to the reduction of biorisk in storage (for example a number of the prescriptive requirements found in 12.3.1).

The CAG recognized that segregated storage requires significant investments, and that clarity on long-term containment requirements to be met for an Interim Certificate of Containment (ICC) – potentially extending into Phase III – is needed now to guide these investments. The CAG acknowledged that a balance needs to be struck between the GAPIII intent of a virtually zero risk of poliovirus release post eradication on one hand, and maintaining sufficient capacity for production and QC of needed vaccines on the other. The CAG discussed the potential eventuality that under such extreme circumstances, the NAC in conjunction with GCC may have the option extended to accept derogations beyond the validity of ICCs, based on a comprehensive risk assessment and detailed justification for such measures. Such derogations should be temporary in nature (i.e. only extended to the time required to secure vaccine supply from fully compliant PEFs) and the NAC/GCC should reassess the risks and benefits of such derogations on a regular basis.

- b. Some areas of misalignment between the draft revision of TRS 926 and GAPIII remain to be addressed. The CAG will provide comments to the draft revision (see Issue 22).
- c. The CAG noted that more specific guidance is needed on the definition of “storage only”, and on containment requirements for areas that are not accessed frequently, such as kill tanks/kill rooms and sample repositories.

CAG recommendations

Modify the recommendation made at the 1st CAG Meeting as follows (new text in **bold**):

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) for an interim certificate of containment (ICC) as well as for a **certificate of containment (CC)** assessment. Any derogations applied for and accepted by the NAC will be reflected on the certificate scope, and associated certificates, **and regularly reassessed**.

Issue 10: RNA

Relevant GAPIII section

Annex 1: Definitions

(a) Poliovirus infectious materials, wild: These include: (...)

(Bullet point 7)

full-length RNA or cDNA that includes capsid sequences derived from wild poliovirus, unless viruses derived from them are demonstrably proven to be 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;

(a) Poliovirus infectious materials, OPV/Sabin: These include: (...)

(Bullet point 7)

full-length RNA or cDNA that includes capsid sequences derived from OPV/Sabin strains;

History

CAG1 recommendation

GAPIII, Annex 1:

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 (e.g., cDNA clone, synthetic transcript).*

Summary of issues raised

- a. IPV vaccine contains an abundance of full length RNA⁸. It does not appear feasible to require handling of IPV RNA in containment.
- b. The scope of facilities using faecal or respiratory secretions samples products derived from poliovirus-permissive cell line materials is incredibly broad (academic, research, etc.) and extensive. Depending on the definition of products derived from polio-permissive cell lines, this could encompass just about all laboratories working with enteroviruses and respiratory viruses. Should certification be required this would have significant implications for affected facilities and resource implications for NACs.

Summary of requests to CAG

The definitions for poliovirus potentially infectious materials need to consider the implementation and the impact.

A copy of the assessment criteria to be used by the WHO’s expert panel for determining the containment requirements for poliovirus full-length RNA or cDNA was requested.

Summary of CAG discussions and conclusions

The CAG noted that full-length RNA is infectious and can be propagated, and therefore constitutes a potential risk when handled outside of containment. The CAG maintains its recommendations that a caution against introducing full length RNA into permissive cells should be included in the definitions of poliovirus infectious materials.

CAG recommendation

The CAG reorganized for clarity the definition developed at the 1st CAG meeting, as follows (reorganized/new text in **bold**):

~~*Poliovirus nucleic acid: Nucleic acid* that has been extracted/purified using methods demonstrated to inactivate poliovirus*~~ ***Poliovirus 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) using methods demonstrated to inactivate poliovirus, or synthesized RNA or cDNA (e.g., cDNA clone, synthetic transcript). Poliovirus nucleic acid 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 in the “Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses”) with or without a transfection reagent, except under appropriate containment conditions as described in GAPIII Annex 2 or Annex 3.***

⁸ Edward T. Mee, Philip D. Minor, and Javier Martin. High resolution identity testing of inactivated poliovirus vaccines. *Vaccine*. 2015 Jul 9; 33(30): 3533–3541. doi: 10.1016/j.vaccine.2015.05.052
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504004/>

~~*"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).~~

Issue 11: Guidance for the establishment of NACs

Relevant GAPIII section

GAPIII Containment Certification Scheme (CCS)⁹
(Endorsed by SAGE and published in October 2016; supersedes Annex 4 of GAPIII).

History

Summary of requests to CAG1

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

CAG1 recommendation

Guidance for the establishment of NACs is available in CCS.

Follow on action required

CAG secretariat to provide clarifications in consultation with individual countries.

Summary of CAG discussions and conclusions

This issue was postponed for discussion at a later meeting.

Way forward

The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 12: 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.

History

CAG1 recommendation

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.

Summary of issues raised

- a. Facilities may not have 10-year-old documents available by the time of the first audit.
- b. Clarification should be provided in terms of when the 10-year period should start.

⁹ Available at: http://polioeradication.org/wp-content/uploads/2017/03/CCS_19022017-EN.pdf

Summary of requests to CAG

- a. Modify this requirement to indicate that all commissioning documents be kept on file for the “lifetime” of the PEF or until 5 years after the PEF is decommissioned. There should be flexibility in implementation.
- b. Clarify when the 10-year period of retention of documents starts.

Summary of CAG discussions and conclusions

Subelement 1.4 of Annexes 2 and 3 requires PEFs to manage records, documents and data that could provide evidence of conformity to the requirements of GAPIII. To do this the PEFs will need to define and implement the controls needed to identify, store, protect, retrieve, retain and destroy records.

The CAG advised that:

- a. The document retention period required in GMP guidelines may differ from that required in GAPIII.
- b. At the time of initial certification the PEFs will not necessarily need to demonstrate at least 10 years of documented records, but will need to demonstrate that they have established effective procedures to ensure appropriate documented records are identified, stored, protected, retained for appropriate periods and how and when they shall be destroyed. If not already in place, the collection and retention of records and documents should start immediately.

CAG recommendation

Modify Subelement 1.4.2 (as updated at the 1st CAG meeting) as follows (new text in **bold**):

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 **are** available for review during ~~national~~ **containment** certification procedures **audits**.*

If not already in place, the collection and retention of records, documents and data should start immediately.

Issue 13: Immunization of facility personnel: maintaining mucosal immunity in facility operators post-OPV cessation

Relevant GAPIII section

Annexes 2 and 3, Subelement 9.2, Vaccination of Personnel

9.2.1 Based on risk, the need for vaccination has been determined and covers groups identified as being potentially exposed to poliovirus.

9.2.2 A vaccination policy has been defined and implemented

9.2.3 Access to laboratories or work is controlled for individuals until they comply with the vaccination policy.

HistorySummary of requests to CAG

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

CAG1 recommendation

Ensure that the SAGE polio working group (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.

Summary of CAG discussions and conclusions

This issue was postponed for discussion at a later meeting.

Way forward

The secretariat will update the CAG on this issue by teleconference or other means in 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Issue 14: Post-exposure protocol

Relevant GAPIII sections

Annexes 2 and 3, Subelement 9.3.1:

A system is established to effectively manage medical and/or environmental emergencies, including but not limited to identifying potentially infected workers and providing immediate medical care to exposed, ill or injured workers.

Annexes 2 and 3, Subelement 10.2.1:

Plans and procedures are established and maintained to:

- 1. identify the potential for incidents and emergency situations involving biological agents, toxins and materials;*
- 2. prevent their occurrence;*
- 3. respond to emergency situations;*
- 4. limit the likelihood of illness or other damage that may be associated with them.*

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.*

History

Summary of requests to CAG1

Address the timing and legality of interventions recommended in GAPIII.

CAG1 Meeting 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.

Summary of CAG discussions and conclusions

The CAG was informed that, as a follow-up to the recommendation made at its first meeting, WHO is developing a post-exposure protocol to identify and deal with individuals, including facility operators, exposed to poliovirus¹⁰ and becoming infected.

It was clarified that the NAC may not have a mandate to oversee national emergency response plans to deal with biohazards. GAPIII requires that the PEFs manage their facility-specific risks, and engage with wider, generic emergency response services as needed in case of a problem.

CAG recommendation

The NAC should demonstrate that there are effective linkages between the response and contingency plans addressing containment breaches in place at the facility and at national level.

Issue 15: The shower

Relevant GAPIII section

Annexes 2 and 3, Subelement 12.3.1 (g):

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).

History

Summary of requests to CAG1

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

CAG1 recommendation

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.

Summary of issues raised

- a. GAPIII requires showering out for both production and laboratories. There should be a distinction between large scale polio manufacturing and small scale polio analytical work (QC and R&D) applying the principles of containment based on risk assessment.
- b. The current draft TRS 926 Annex 2 allows the use of BSC class II to protect operators and the environment in BSL 3. The air from the BSC class II is directed through HEPA filters when samples with live poliovirus are handled. Is this an example of a closed system with validated primary containment where showering out would not be mandatory?

For safety, quality and practical reasons, it is not possible to perform quality control testing of inactivated polio vaccines in a Class III BSC or isolator. For laboratory work a Class II BSC in combination with full PPE including respirators should provide sufficient protection against contamination of the worker and laboratory apparel.

- c. A validated Shower SOP should be considered.

¹⁰ WHO-POL. *Public Health Management of a Breach of Type 2 Poliovirus Containment*. Draft document.

- d. Safe removal of full-body covering PPE could reach the same biocontainment objective as showering out. In case of a spill a local risk assessment may determine that a chemical decontamination of the PPE prior to exit would suffice.
- e. This requirement does not state that the walk-through exit shower is a body-shower. Can a walk-through shower be a chemical shower?
- f. Circumstances that may require the use of an exit shower may not exist in every proposed PEF. The GAPIII requirement does not take into consideration the specific risks of each facility and the activities performed therein.
- g. Requiring a body shower with no effluent decontamination does not contain the poliovirus within the laboratory and creates an additional risk of contamination of the egress water and drain system.

Summary of requests to CAG

- a. Differentiate between large scale manufacturing and small scale analytical work.
- b. Consider the use of Class II BSCs in combination with full PPE in facilities employing closed systems demonstrating validated primary containment.
- c. Require exit showering only in case of major spills.
- d. Develop a shower SOP.
- e. Clarify what is meant by a walk-through shower.
- f. Determine the need for showering out through risk assessment, based on procedures, types, volumes and concentrations of PV materials used in each PEF.
- g. Require that the shower be connected to the effluent treatment plant.

Summary of CAG discussions and conclusions

- a. Multiple factors would need to be considered in distinguishing between “large scale” and “small scale” work, including but not limited to volume, type and titre of infective material handled.
- b. More data are needed on PPE as a possible source of infectious organisms. The CAG agreed to keep the current precautionary approach until evidence is available to justify an alternative approach.
- c. The CAG considers that any decision to omit routine showering out should be supported by a documented risk assessment.
- d. The CAG agreed that the use of a shower SOP is good practice. Shower SOPs should be facility-specific and should be developed by the PEF.
- e. The shower would typically be a water shower, used in line with the facility’s shower SOP.
- f. The shower should be connected to an effluent inactivation procedure.

In conclusion, the CAG agreed to consider the feasibility of using risk assessments to justify the omission of routine showering-out when leaving the containment perimeter.

CAG recommendation

The GAPIII requirements in Subelement 12.3.1 (g) of Annexes 2 and 3, as modified at the 1st CAG meeting, were not changed.

The CAG assigned a subgroup to the task to review the issue of mandatory showering, consider the information and evidence around the need/benefits of shower-out (including adherence to the precautionary principle to minimize the risk of release of poliovirus post eradication to as close as possible to zero), and evaluate whether or not a robust set of criteria could be developed for use in risk assessments to justify the omission of routine showering-out. The CAG agreed to discuss this issue by teleconference in January 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

Way forward

A subgroup of CAG members (Dr Jagadish Deshpande, Dr Vibeke Halkjær-Knudsen and Dr Åsa Szekely Björndal) will work with the secretariat to review the issue of mandatory showering, consider the information and evidence around the need/benefits of shower-out (including adherence to the precautionary principle to minimize the risk of release of poliovirus post eradication to as close as possible to zero), and evaluate whether or not a robust set of criteria could be developed for use in risk assessments to potentially justify the omission of routine showering-out, and will present these to CAG at its first teleconference in January 2018.

Issue 16: Dedicated facilities, work on campaign basis

Relevant GAPIII section

Annexes 2 and 3, Subelement 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.

Other relevant text: Draft revision of TRS 926, Annex 2, Point 4.1.2:

Whenever possible, polio vaccine production facilities where live poliovirus is processed should be in dedicated buildings. If they are located in multipurpose buildings, the polio vaccine production facility must have separate entrances and exits for personnel and materials, (...).

History

CAG1 recommendation

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) of Annexes 2 and 3 was not changed.

Summary of issues raised

- a. The GAPIII requirement applies to both large scale polio manufacturing and small scale polio analytical work (QC and R&D). Investment in a fully dedicated QC laboratory is not scientifically justified.
- b. The draft TRS 926 is not aligned with GAPIII. The draft TRS 926 requires separation of entrance and exit for personnel in multi-agent facilities handling poliovirus. It is argued that containment can be supported by trending environmental monitoring data.
- c. If all materials, equipment, and waste are treated as though they contain poliovirus in accordance with GAPIII, the risks are mitigated and dedicated facilities are not required.

Summary of requests to CAG

- a. Distinguish between large scale polio manufacturing and small scale polio analytical work (QC and R&D) applying the principles of risk management.
- b. Align the draft TRS 926 and GAPIII.
- c. Clarify the definition of “poliovirus dedicated facilities”. Expand “dedicated” to reflect a time or spatial containment. Allow use of a performance-based containment method.

Summary of CAG discussions and conclusions

The CAG recognized the challenges of maintaining dedicated QC laboratories for work on poliovirus only. At its 1st Meeting the CAG had recommended a flexible, risk-based approach to the implementation of this requirement in Phase II of GAPIII. However, recognizing that the objective of GAPIII is to minimize the risk of release of poliovirus in the post-eradication world to as close as possible to zero, the CAG advised not to extend the flexibility allowed in Phase II into Phase III.

Inconsistencies between the draft TRS and GAPIII will be addressed as part of the revision of the draft TRS 926 Annex 2 (see Issue 22).

CAG recommendation

Subelement 12.3.1 (c), of Annexes 2 and 3 was not changed.

Issue 17: Dedicated air supply

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.

History

CAG1 recommendation

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) of Annex 2 was not changed.

Summary of issues raised

- a. Where functional and validated back-flow protection is present on the supply system, a dedicated ventilation system for the exhaust from the containment area system should suffice.
- b. Terminal HEPA filters at the containment barrier meet the intent of this requirement.

Summary of requests to CAG

- a. Clarify the requirement by stating that the dedicated ventilation system applies to all 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.
- b. Clarify the definition of “dedicated ventilation system”. Does this mean that the facility must have its own dedicated fans, or can they be fans used for other contained spaces provided there is a means of isolation of the ductwork (HEPA filters or other backflow protection)?

Summary of CAG discussions and conclusions

CAG members commented that HEPA filters only provide protection as long as they do not fail, and that the risk minimization effect depends on the quality of the engineering, maintenance and management systems of the facility as a whole. The facility must have its own dedicated fans, and these cannot be shared with other contained spaces even if the ductwork is provided with HEPA filters or other backflow protection devices.

There is no requirement for a dedicated air system maintaining directional airflow for work with WPV2 and OPV2/Sabin2 poliovirus materials during Phase II and for work with OPV2/Sabin2 poliovirus materials in Phase III of GAPIII, as described in Subelement 12.3.1 (h) of Annexes 2 and 3. The text ‘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’ only applies to work with WPV in Phase III, where the objective of GAPIII is to minimize the risk of release of poliovirus post eradication to as close as possible to zero.

CAG recommendation

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

Issue 18: Ventilation system and backflow protection/prevention**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.

History**CAG1 Meeting recommendations**

Gas lines are not always pressurized. For this reason, a backflow protection should always be there. Subelement 12.3.1 (i) of Annex 2 was not changed.

Summary of issues raised

- a. No backflow protection is necessary on gas services as these are always pressurized.
- b. Backflow devices are not compatible with GMP clean fluid network design due to their inherent dead spaces.

Summary of requests to CAG

- a. Remove the requirement for backflow protection on gas services, or add: "... (water, gases which are unpressurized)..."
- b. Allow a decision whether to install backflow devices or not according to a risk analysis.

Summary of CAG discussions and conclusions

- a. The CAG clarified that gas lines can become depressurized.
- b. The CAG noted that the GAPIII requirement is consistent with TRS 926 Annex 2, which requires that all liquid and gas services to the containment area must be protected from back flow based on risk assessment. The CAG was not aware of a GMP-related risk that would justify changing the GAPIII requirement. Facility-specific solutions for its implementation will be assessed as part of the certification process.

CAG recommendation

The CAG recommended to modify Subelement 12.3.1 (i) in Annex 2 (under "Requirements for Final Containment of all WPV") as follows (new text in **bold**):

*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 **passing across the polio containment boundary (liquids, gases)** and via measures to prevent release through traps, sinks and shower drains.*

Issue 19: Effluent decontamination

Relevant GAPIII sections

Subelement 12.3.1 (i) in Annex 2 (under “Requirements for Containment of WPV2”) and in Annex 3: *Throughout the Poliovirus type 2 containment period, a dose of IPV will be introduced, high global vaccine coverage will be maintained (population immunity is not expected to decline) and the use of mOPV2 for outbreak response is considered. Where evidence of satisfactory implementation of primary and secondary safeguards (described in GAPIII) is provided, decontamination of effluents is not required.*

Summary of issues raised

The last sentence of Subelement 12.3.1 (i) is contradictory: Decontamination of effluents is itself a part of primary safeguards, so it will always be required. Decontamination of effluents is also required in Subelements 14.1.1 and 14.1.3 and in Table 1 of the Strategy section under “Decontamination of materials/equipment” and under “Dedicated effluent treatment plant” (see Footnote 3).

Summary of requests to CAG

Delete the above-mentioned clause in Annexes 2 and 3, Subelement 12.3.1 (i) and replace it with text of that Subelement applicable to final containment of all WPV in Annex 2:

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.

Summary of CAG discussions and conclusions

The CAG agreed that the current GAPIII requirements are inconsistent. It was noted that effluent decontamination is also required in Subelement 12.3.1 (j) (“The decontamination of all materials exiting the facility is achieved through a validated sterilization/decontamination procedure”).

The CAG recognized that implementing effluent decontamination may be challenging for some facilities. Designated PEFs can apply for an ICC, describing their plans and expected timelines to meet the requirement, and/or demonstrate through a risk/benefit analysis that the solution in place at the facility meets the intent of the requirement.

CAG recommendation

The CAG recommended to modify Subelement 12.3.1 (i) in Annex 2 (under “Requirements for Containment of WPV2”) and in Annex 3 as follows (new text in **bold**):

~~*Throughout the Poliovirus type 2 containment period, a dose of IPV will be introduced, high global vaccine coverage will be maintained (population immunity is not expected to decline) and the use of mOPV2 for outbreak response is considered. Where evidence of satisfactory implementation of primary and secondary safeguards (described in GAPIII) is provided, the decontamination of effluents is not required.*~~

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 passing across the polio containment boundary (liquids, gases) and via measures to prevent release through traps, sinks and shower drains.

In other terms, this recommendation clarifies that:

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.

Issue 20: Dedicated effluent treatment plant**Relevant GAPIII section**

Strategy, Table 1 (extract)

	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

Footnote 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).*

Summary of issues raised

Table 1 and the associated Footnote 3 require clarification: Does 'No³' mean that an effluent treatment plant is not required, or does it mean that the effluent treatment plant does not need to be dedicated?

Effluent treatment is required in Annexes 2 and 3, Subelements 14.1.1 and 14.1.3.

The 2nd draft TRS 926 (4.4.1, page 16, line 4) requires 'Decontamination of solid, liquid and gaseous wastes should take place within the containment area'.

Summary of requests to CAG

Amend the wording in Table 1 to clarify that an effluent treatment plant is always required, and that it should be dedicated in the final containment period for all wild polioviruses.

Provide comments to the draft TRS 926.

Summary of CAG discussions and conclusions

The CAG accepted the request. It was clarified that effluent treatment could be achieved by a variety of methods, as reflected in Footnote 3 to Table 1.

The issue about whether or not the kill tank area should be contained will be discussed at a CAG teleconference in 2018, as described under Issue 22 below.

CAG recommendations

The CAG recommended to modify the line on effluent treatment and its associated Footnote 3 in Table 1 as follows:

~~Dedicated~~ Effluent treatment plant: ~~No~~ Not dedicated³ / ~~No~~ Not dedicated³ / ~~Yes~~ Dedicated⁴

~~Footnote 3: Untreated release into a closed sewage system with secondary effluent treatment in the facility location (all~~ **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).**

Issue 21: Guidance for non-poliovirus facilities

Relevant GAPIII section

Strategy, Phase implementation

Relevant submission

Guidance document developed by the Guidance Drafting Group (GDG) ¹¹

History

Summary of requests to CAG1

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

CAG1 discussions

A first draft of a guidance document for non-poliovirus facilities retaining potentially infectious samples was presented to the CAG at its 1st Meeting.

CAG1 Meeting 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.

Follow-on action

The draft guidance was posted on the website of the Global Polio Eradication Initiative on 4 September 2017 for public comment ¹².

Summary of issues raised

Consider the impact on the NAC if certification of facilities retaining potentially infectious materials is required.

Summary of requests to CAG

Clarify whether NACs will be asked to certify facilities handling different types of PIMs.

Presentation of draft guidance

Dr Bruce Thorley presented the draft guidance for non-poliovirus facilities to the CAG on behalf of the GDG. Non-poliovirus facilities are those that are not working on polioviruses, but that may have potentially infectious materials in their possession from clinical or environmental work in places where wild or vaccine-derived polioviruses were circulating, or where OPV was being used.

The guidance sets a strategic goal of retaining no WPV/cVDPV potentially infectious materials (PIM) outside of PEFs and encourages facilities to set a high bar when deciding to retain such materials.

The guidance currently applies to all type 2 PVs, but it can already be used to address type 1 and 3 PV PIMs. After eradication of types 1 and 3 is certified, the guidance will apply to all polioviruses.

Facilities planning to retain samples potentially infectious for WPV2/cVDPV2 are subject to the designation as PEF by the responsible national authority (e.g. Ministry of Health) and the approval of the responsible NAC through the GAPIII certification process. Facilities retaining OPV/Sabin PV PIM are not subject to designation as PEF and NAC certification, but must declare their holdings to the responsible national authority (e.g. Ministry of Health) and maintain an accurate inventory of materials in their possession. The guidance proposes risk-appropriate management standards for OPV/Sabin PV PIM.

Dr Steve Oberste presented data on the estimated number of samples containing PIMs in collections worldwide, based on testing of selected sample collections for poliovirus. PV isolation rates vary depending on when and where samples were collected, the type of sample and the age of the

¹¹ *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*. Draft for CAG: 20 Nov 2017

¹² Available at: <http://polioeradication.org/wp-content/uploads/2016/07/guidance-for-PIM-4-sep-2017.docx>

subjects¹³. Only relatively few of the samples tested were found to contain poliovirus, and the numbers are expected to decrease as polio eradication progresses.

Summary of CAG discussions and conclusions

The CAG welcomed this much-needed guidance and provided some comments on the second draft.

CAG recommendation

The CAG adopted the *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*, subject to amendments in a final round of comments to be provided by CAG members within a week of the 2nd CAG meeting. The CAG recommended that the guidance be published and distributed to relevant national authorities as soon as possible.

Way forward

CAG members will provide a final round of comments by 8 December 2017. Once these comments have been addressed, the guidance will be accepted as endorsed by the CAG.

Issue 22: TRS 926

Relevant submission

Draft revision of WHO Technical Report Series (TRS), Annex 2.¹⁴

Summary of issues raised

The draft TRS 926 Annex 2 has been revised to be consistent with GAPIII.

Summary of requests to CAG

Review the draft and provide comments

Presentation of draft revision

Dr Insoo Shin presented the draft revision to the CAG on behalf of the TRS drafting group. The revision was undertaken to align TRS 926 Annex 2 with GAPIII. Some remaining areas in need of alignment with GAPIII were highlighted in the draft.

The draft revision will be posted on the WHO website for a first round of public consultation at the end of 2017 or in early 2018. A revised draft will be discussed at a consultation of experts, followed by a second round of public consultation at the end of June 2018. The final draft will be submitted to the WHO Expert Committee on Biological Standardization (ECBS) in October 2018 for endorsement.

Summary of CAG discussions and conclusions

The CAG provided some comments on the draft revision. It was noted that this draft TRS Annex 2 guides the production of WHO-prequalified polio vaccines, and alignment with GAPIII is therefore crucial. The two documents are complementary in that TRS 926 guidance focuses on GMP issues, while GAPIII focuses on biosafety and biosecurity issues.

CAG recommendation

The CAG welcomed the revision of TRS 926 Annex 2 to align it with GAPIII, committed to providing its consolidated comments as soon as possible, and planned to discuss this issue further at a CAG teleconference in January 2018.

Way forward

The secretariat will draft and circulate to CAG members a list of areas where alignment between the draft TRS 926 Annex 2 and GAPIII needs to be improved. The CAG's comments on the revision of TRS 926 Annex 2 will be consolidated in a teleconference in January 2018. Results of CAG discussions on this issue and associated CAG recommendations will be reported and published on the web.

¹³ See Annex 1 of the draft *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*

¹⁴ WHO Technical Report Series 926, Annex 2. *Guidelines for the safe production and quality control of poliomyelitis vaccine*. (2nd draft version 6 November 2017).

Other issues discussed at the 2nd CAG meeting

Responsibilities for GAPIII-related decisions

The CAG and the SAGE both advise the WHO Director-General on poliovirus containment-related matters. It was suggested that CAG may advise on facility containment-related GAPIII requirements (primary and tertiary safeguards), while SAGE may advise on secondary safeguards. The CAG Chair will meet with the SAGE Chair to reach an informal agreement on the roles of the two advisory groups in making GAPIII-related decisions.

Communicating GAPIII changes

A user-friendly process is needed to record and communicate CAG recommendations, including both advice on GAPIII implementation and recommended changes to the wording of GAPIII. Following advice from the WHO Legal Office, the secretariat will develop a process to record CAG's recommendations addressing GAPIII.

Date of next meeting

The following topics and timelines were identified for CAG discussions by teleconferences: (1) Shower, TRS 926 revision (January 2018); and (2) Novel strains and new technologies (February/March 2018). Results of CAG discussions and associated CAG recommendations will be reported and published on the web.

The 3rd CAG Meeting is planned to be held in April 2018. The date will be confirmed in early 2018.

Annex 1: Abbreviations

BSC	Biosafety cabinet
BSL	Biosafety level
CAG	WHO's Containment Advisory Group
CCS	GAPIII Containment Certification Scheme
CC	Certificate of Containment
ICC	Interim certificate of containment
CP	Certificate of participation
CWG	GCC's Containment Working Group
ECBS	WHO's Expert Committee on Biological Standardization
ESG	Expert Support Group
GAPIII	Global Action Plan III for Poliovirus Containment
GCC	WHO's Global Commission for the Certification of the Eradication of Poliomyelitis
GDG	Guidance Drafting Group
GMP	Good manufacturing practice
GMT	Good microbiological technique
GPEI	Global Polio Eradication Initiative
GPLN	Global Polio Laboratory Network
HEPA	High-efficiency particulate arresting, or high-efficiency particulate air
IHR	International Health Regulations
IPV	Inactivated polio vaccine
NAC	National authority for containment
NCC	National Certification Committee for Poliomyelitis Eradication
NRA	National regulatory authority
OPV	Oral polio vaccine
bOPV	Bivalent oral polio vaccine (containing two poliovirus types)
mOPV	Monovalent oral polio vaccine (containing one poliovirus type)
nOPV	New oral polio vaccine
PEF	Poliovirus-essential facility
PIM	Potentially infective material
POL	WHO's Polio Eradication Department
PPE	Personal protective equipment
PRC	Polio Research Committee
PV	Poliovirus
QC	Quality control
RCC	Regional Certification Committee for Poliomyelitis Eradication (one for each WHO region)
RNA	Ribonucleic acid
SAGE	WHO's Strategic Advisory Group of Experts on Immunization
TRS	WHO Technical Report Series
VDPV	Vaccine-derived poliovirus
VLP	Virus-like particle
WG	Working group
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild poliovirus