

An outline of the Global Action Plan

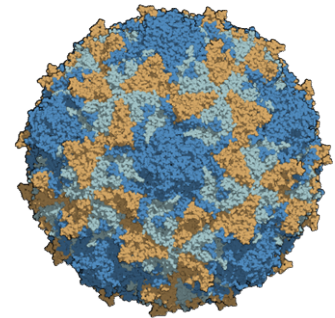
to minimize poliovirus facility-associated risk
after type-specific eradication ...
(2015)

GAP III

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DCVMN August 2017

The situation today:

Wild type polio is nearly eradicated.
Type 2 polio is eradicated.



The type 2 component of Oral Polio Vaccine (OPV) was withdrawn
in 2016 (tOPV withdrawn, replaced by bOPV)

Now, protection from type 2 Poliovirus depends on the use of
Inactivated Polio vaccine (IPV)



Vaccine: <https://www.cdc.gov/polio/about/>

Virus: Filman, D.J., Syed, R., Chow, M., Macadam, A.J., Minor, P.D., Hogle, J.M. (1989) EMBO J. 8: 1567-1579.

Containment of polio virus is needed:

1. In 2014 GSK discharged 45 litres of live type 3 poliovirus into the river (about 10^{13} pfu).
2. In 2017 two workers in a vaccine plant in the Netherlands were exposed to **wild type 2** poliovirus. One became infected and excreted virus for 29 days. The virus was detected in sewage.

Containment of **type 2** poliovirus for all purposes is particularly needed.

Polio vaccine production particularly needs to be contained.

Documents:

1. Polio Eradication and Endgame Strategic Plan 2013-2018

2. Global Action Plan (3rd Edition) [GAPIII] 

or

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.

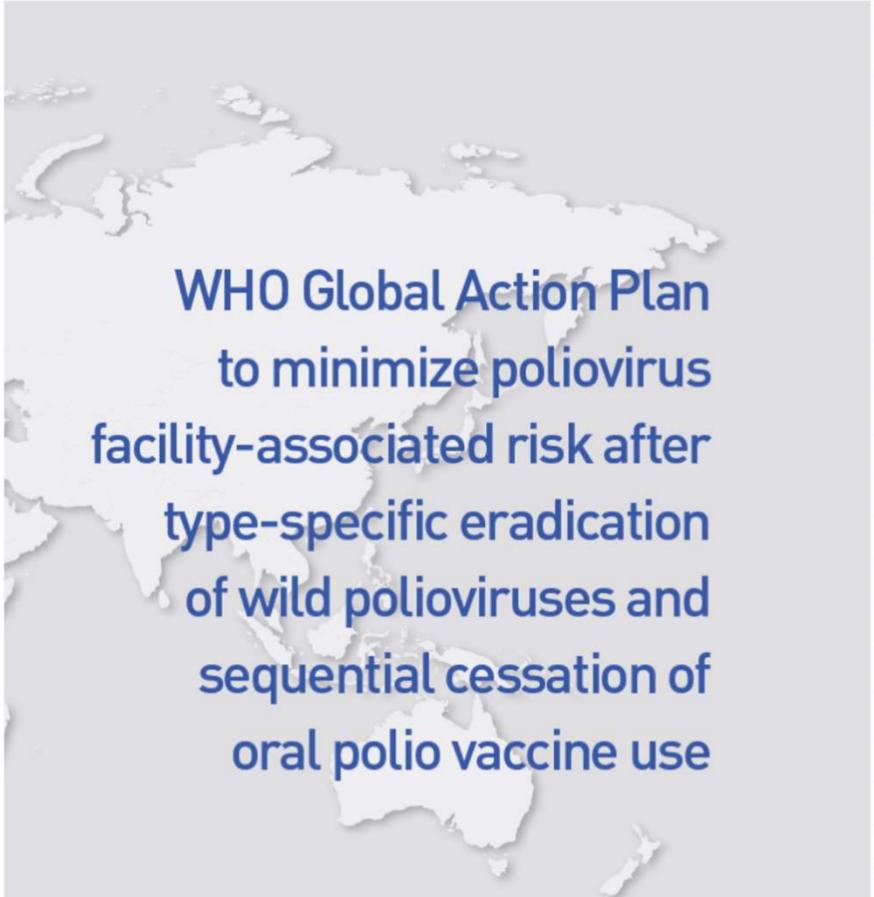
3. Containment Certification Scheme (CCS)

see <http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/containment/>

Other documents of interest related to vaccine manufacture:

Guidelines on IPV manufacture; Guidelines on Oral Polio Vaccine manufacture; GMP guidelines; TRS 926: making IPV safely post eradication

*This discussion is limited to **GAPIII** to begin with. It is a complicated document. Some of it is for clinical laboratories only and the structure will be presented.*



**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



Introduction	1
Rationale	3
Strategy	4
Risk elimination	4
Biorisk management	4
Overview of phases	7
Phase I: Preparation for containment of poliovirus type 2	7
Phase II: Poliovirus type 2 containment period	7
Phase III: Final poliovirus containment	8
Phase implementation	10
Phase I: Preparation for containment of poliovirus type 2	10
Phase I: Inventory, destruction, preparation for poliovirus type 2 containment	10
Phase II: Poliovirus type 2 containment period	13
Phase IIa: Containment of WPV2	13
Phase IIb: Containment of OPV2/Sabin2 poliovirus	13
Phase III: Final poliovirus containment	16
Phase IIIa: Final containment of all WPV	16
Phase IIIb: Final containment of all OPV/Sabin polioviruses	16
Bibliography	20
Annexes	21
Annex 1: Definitions	22
Annex 2: Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials	28
Annex 3: Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)	101
Annex 4: WHO verification that certified poliovirus-essential facilities comply with GAPIII	170
Annex 5: Risk assessment strategy	172
Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus material in poliovirus-non-essential facilities	173

GAP III structure:

1. Introduction
2. Rationale
3. Strategy
 - Risk elimination/management
4. Phases (inventory, containment)

Annexes 1-6

GAPIII will not be revised for another three years at least.

Note that there are sections of annex 2 and 3 that are **required**.

At the moment risk assessment cannot justify alternative approaches. Risk assessment makes no difference to the need to comply.

Acknowledgements

Abbreviations and acronyms

Introduction

Rationale

Strategy

Risk elimination

Biorisk management

Overview of phases

Annex 1: Definitions

Annex 2: Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials

Annex 3: Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)

Annex 4: WHO verification that certified poliovirus-essential facilities comply with GAPIII

Annex 5: Risk assessment strategy

Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus material in poliovirus-non-essential facilities

GAP III structure:

The Introduction and Rationale cover the current and predicted progress in the phases of eradication.

They describe features of polio virus infections that explain the reason for the steps which must be taken to contain the virus.

Poliovirus may escape from a facility either through a spill, accidental discharge or through infection of a worker.

The risks are to the environment (the general population) not to the worker. The specific worker can be protected by vaccination.

Acknowledgements

Abbreviations and acronyms

→ Introduction

→ Rationale

Strategy

Risk elimination

Biorisk management

Overview of phases

GAP III structure:

Strategy

Risk elimination vs risk management.

1. Risk elimination: stop working on polio (preferred option)
2. Risk management:
 - i) primary (facilities and practices)
 - ii) secondary (immunisation coverage)
 - iii) tertiary (good infrastructure)

Acknowledgements

Abbreviations and acronyms

Introduction

Rationale

→ Strategy

Risk elimination

Biorisk management

Overview of phases



GAP III structure:

Strategy

Risk elimination

- The number of laboratories working with polio virus in the UK has fallen from >50 to about 4.
- [Risk elimination cannot be applied to vaccine manufacture where virus growth is needed.](#)
- In addition there are regulatory documents (e.g. disinfection BSI documents, quality tests of immunoglobulins in the USA) that specify the use of poliovirus in tests. Some now specify the use of vaccine strains but when eradication is declared this will not be enough. The documents should be changed to remove the requirement for polio. This has not been done yet.

Acknowledgements

Abbreviations and acronyms

Introduction

Rationale

Strategy



Risk elimination

Biorisk management

Overview of phases

GAP III structure:

Phases

Containment will develop as polio is eradicated.

For example:

- Type 2 poliovirus is eradicated so it must be rigorously contained. It has been withdrawn from OPV.
- - Type 3 has not been seen since 2012, but has not been declared eradicated. It does not have to be contained yet, but it will do so in the near future.
- Type 1 will be the last.

A timetable is given, for instance possibly to stop all OPV and therefore contain all poliovirus by 2020.

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Abbreviations and acronyms

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Rationale

Strategy

Risk elimination

Biorisk management

 Overview of phases

GAP III structure:

Annexes

Annex 1: Definitions

Annex 2: Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials

Annex 3: Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)

Annex 4: WHO verification that certified poliovirus-essential facilities comply with GAPIII

Annex 5: Risk assessment strategy

Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus **material** in poliovirus-non-essential facilities

Annexes 2 and 3 are particularly important for manufacturers

Annexes	21
Annex 1: Definitions	22
Annex 2: Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials	28
Annex 3: Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)	101
Annex 4: WHO verification that certified poliovirus-essential facilities comply with GAPIII	170
Annex 5: Risk assessment strategy	172
Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus material in poliovirus-non-essential facilities	173

GAP III structure:

Annex 1 Definitions: What does GAPIII apply to?

1. Wild type viruses are defined as those that have circulated and caused polio epidemics. They include the strains used in making **Salk IPV**. Circulating Sabin vaccine derived viruses (**cVDPVs**) are in the same category as are any vaccine viruses not licensed for use (CHAT, Cox, USOL D Bac.)

New safer strains are treated as wild type pending separate consideration on how to handle them.

2. Vaccine viruses are **Sabin** vaccine strains less than 1% drifted in sequence.

*This applies **Sabin vaccine viruses** from patients or the environment.*

Sabin vaccine strains for production of sIPV are different. They must be grown carefully so that they do not become virulent which they can do with far less sequence drift.

GAP III structure:

Annex 1 Definitions: What does GAP III apply to?

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

- clinical materials from confirmed wild poliovirus (including VDPV) infections;
- environmental sewage or water samples that have tested positive for the presence of wild polioviruses;
- cell culture isolates and reference strains of wild poliovirus;
- **seed stocks and infectious materials from IPV production;**
- infected animals or samples from such animals, including human poliovirus receptor transgenic mice;
- derivatives produced in the laboratory that have capsid sequences from wild polioviruses, unless demonstrably proven to be safer than Sabin strains. The safety of new derivatives containing wild poliovirus capsid sequences will be assessed by an expert panel, 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;
- 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;
- cells persistently infected with poliovirus strains whose capsid sequences are derived from wild poliovirus.

GAP III structure:

Annex 1 Definitions: What does GAPIII apply to?

(b) 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.

GAP III structure:

Annexes 2, 3, and 6

- Annexes 2,3 and 6 in GAP III describe a Safety Quality Management system with **16 separate elements**.
- It is based on CWA15793 *Laboratory risk management*. This is an International non WHO document)
- Mostly this addresses Quality Assurance, written procedures, roles and responsibilities rather than technical virological matters.

Annexes	21
Annex 1: Definitions	22
→ Annex 2: Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials	28
→ Annex 3: Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)	101
Annex 4: WHO verification that certified poliovirus-essential facilities comply with GAP III	170
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→ Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus material in poliovirus-non-essential facilities	173

GAP III structure:

Annexes 2 and 3

- Annex 2 covers working with wild type viruses, and
- Annex 3 deals with **vaccine viruses**. They are divided into **requirements** (which you must comply with) and **guidance notes** (which suggest how to meet the requirements).

The two annexes are very similar and require a major management structure and a very high level of containment overseen and audited by a system with WHO at its head to verify it.

They contain requirements for facilities
*(air handling, effluent treatment,
containment within a facility, shower out,
storage of materials etc).*

These can make production and testing more difficult.

At the moment a risk assessment cannot justify not meeting requirements.

Annex 1: Definitions

→ **Annex 2:** Biorisk management standard for poliovirus-essential facilities holding wild poliovirus materials


→ **Annex 3:** Biorisk management standard for poliovirus-essential facilities holding only OPV/Sabin poliovirus materials (no WPV)

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ANNEX 2: BIORISK MANAGEMENT STANDARD FOR POLIOVIRUS-ESSENTIAL FACILITIES HOLDING WILD POLIOVIRUS MATERIALS

CWA15793 Clause No. ¹⁸	Biorisk Management Element No.	Requirements for Containment of WPV2	Requirements for Final Containment of all WPV	Guidance
CWA 4.4.5.3	10.4.1 	Structured and realistic emergency exercises and simulations, including security drills, are conducted at regular intervals based on risk, to test the plans, prepare personnel and learn from any good practices or deficiencies identified.		<p>Exercises and simulations should be conducted to provide assurance that plans are effective and to learn from any lessons that arise.</p> <p>Exercises should be planned and every effort made to ensure they realistically represent the events simulated. However, such activities should also be conducted under controlled conditions and not be allowed to become a source of risk in their own right. The results of an exercise should be documented and reviewed for lessons learnt, and feedback on performance should be provided to the appropriate personnel. Any resulting actions should be recorded and allocated to named individuals, and measures should be put in place to ensure they are closed out effectively.</p>
	10.5	Contingency Plans		
CWA 4.4.5.4	10.5.1	In the event of an emergency, adequate contingency measures are in place to ensure the safety and security of continued operations.		Normal operating conditions may be disrupted in the event of an emergency or unforeseen event. This could range from safely shutting down work during a power failure, to obtaining alternative storage conditions in the event of a breakdown. Such eventualities should be considered proactively, and contingency plans put in place. Activities should address the need for adequate redundancy, replacement and other measures, which could involve the availability of alternative facilities or personnel, the introduction of backup systems (e.g. power supplies), alternative means of decontaminating materials in the event of the failure of critical systems or equipment (e.g. kill tanks or autoclaves), or the complete safe shutdown of operations in extreme situations.

ANNEX 2: BIORISK MANAGEMENT STANDARD FOR POLIOVIRUS-ESSENTIAL FACILITIES HOLDING WILD POLIOVIRUS MATERIALS

CWA15793 Clause No. ¹⁸	Biorisk Management Element No.	Requirements for Containment of WPV2	Requirements for Final Containment of all WPV	Guidance
	12.3	Infrastructure and Operational Management		
CWA 4.4.4.8	12.3.1 	<p>Facilities, equipment and processes are designed and run in a safe and secure way with respect to biorisk management.</p> <p>The poliovirus facility incorporates features that are guided by assessments of the risk of poliovirus reintroduction in the community and includes the following provisions:</p> <ol style="list-style-type: none"> Poliovirus facilities are located in countries with demonstrated high national immunization coverage (= DTP3 coverage). Poliovirus facilities are located in areas with closed sewage systems with secondary or greater treatment of effluents. 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. 	<p>Facilities, equipment and processes are designed and run in a safe and secure way with respect to biorisk management.</p> <p>The poliovirus facility incorporates features that are guided by assessments of the risk of poliovirus reintroduction in the community and includes the following provisions:</p> <ol style="list-style-type: none"> Poliovirus facilities are located in countries with demonstrated high national immunization coverage (>90%). 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. 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. 	

GAP III structure:

Annex 6

- Annex 6 describes the system for the safe handling of new samples potentially containing poliovirus material i.e. where you do not know it is contaminated.
- It relates to polio surveillance laboratories only.
- It does not relate to other clinical diagnostic laboratories
- WHO is not involved unless a poliovirus is identified but the management structures and philosophy are the same as for Annexes 1 and 2.
- Annex 6 is not prescriptive; it is truly based on risk assessment of the activities by the laboratory concerned. Control would be at national level. If true this makes environmental surveillance easier.

Annex 1: Definitions

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Annex 6: Biorisk management standard for safe handling of new samples potentially containing poliovirus material in poliovirus-non-essential facilities

Of interest:

There is no legal basis for the enforcement of GAP III.

- It was endorsed by **WHO SAGE** and by the **World Health Assembly**.
- This means that **health ministers** have endorsed it.
- The **Health and Safety Executive in the UK** have taken on the responsibility for it and consider that they have a moral duty to support and implement it
 - They have reclassified type 2 poliovirus from category 2 to category 3.
 - This is nearly what is required by GAP III and is supported by legislation.

GAP III implementation committees:

- Global Certification Commission (GCC)
- Containment Working Group (CWG)
- National Authority for Containment (NAC)
- Containment Advisory Group (CAG)



Other abbreviations:

- CCS: containment certification scheme
- PEF: polio essential facility
- CP: certificate of participation
- ICC: interim certificate of compliance
- ICC-SC: interim certificate of compliance-specific non-conformity
- CC: certificate of compliance

Polio vaccine manufacturers:

- Manufacturers of polio vaccines have stated that they are not GAPIII compliant and cannot become so in the short term without disruption of supply.
- All claim that they will be compliant.



In conclusion:

- GAPIII is a complex document covering a very wide range of activities where polio might be a risk.
- The actions that follow in specific instances are not always clear although vaccine production for instance must be addressed.
- It has discouraged work on poliovirus which is probably a good thing in the long run.

GAP III