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Report of CAG TC3 on nOPV2 candidate vaccines and S19- poliovirus type 2 strains
7 June 2018

List of Abbreviations:

CAG	Containment Advisory Group
ESG	Expert Support Group
GMO	Genetically Modified Organism
IPV	Inactivated Poliomyelitis Vaccine
mOPV2	Monovalent Oral Poliomyelitis Type 2 Vaccine
MOH	Ministry of Health
nOPV2	Novel Oral Poliomyelitis Type 2 Vaccine
NAC	National Authority for Containment
NCC	National Certification Commission for the Eradication of Poliomyelitis
NPCC	National Poliovirus Containment Coordinator
NRA	National Regulatory Authority
OPV	Oral Poliomyelitis Vaccine
R_0	Reproductive rate
RCC	Regional Certification Commission for the Eradication of Poliomyelitis
RT-rtPCR	Real-time reverse transcriptase polymerase chain reaction
TgPVR	Transgenic mice expressing the cell receptor for poliovirus
TC	Teleconference
VDPV	Vaccine-derived Poliovirus
WHO	World Health Organization
WPV	Wild Poliovirus

Participants:

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Background

CAG TC3 was held as a follow-up to CAG TC2[1] which was convened in March 2018. Applying the criteria for the evaluation of improved 'safety' of new poliovirus strains (see next section), Dr Mark Pallansch presented on behalf of the ESG their recommendations (Annex 1) for CAG to conclude on:

1. Criteria for evaluating improved 'safety' of novel poliovirus strains
2. Containment requirements of nOPV2 candidate vaccines and S19-poliovirus type 2 strains
3. Impact of proposed use of these strains on the containment requirements

[1] Report of Teleconference of the Containment Advisory Group (CAG TC2) on Novel Poliovirus Strains, 8 March 2018. Available at: http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/

Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling

The development of the criteria to evaluate the 'safety' of novel poliovirus strains or other related strains are based on the following assumptions:

1) The properties of the strains under evaluation are referenced to the corresponding Sabin strains
2) There is no change implication to Annex 3 of GAPIII for facilities handling only OPV/Sabin poliovirus infectious materials
3) The recognition of the need to define an essential minimal information and data set required for the evaluation of such strains
4) The criteria developed, relevant to the safety aspects of a containment risk assessment, should be widely useful for the evaluation of any other novel or related poliovirus strains

The possible criteria and data sources for the evaluation of improved 'safety' of novel poliovirus strains and other related strains should include but not limited to the following:

A. Novel poliovirus strain properties

1) Genetic stability to loss of attenuation – conditions
    a. Theoretical
    b. Cell culture (e.g., serial passage)
    c. Animal studies (e.g., single, multiple passage)
    d. Characterization (phenotype, genotype)
2) Neurovirulence – degree of attenuation
    a. Theoretical
    b. Cell culture
    c. Animal studies
        i. TgPVR mice
        ii. Non-human primates
3) Replicative fitness – proxy for infectiousness
    a. Cell culture yield (single cycle; infectivity measure)
    b. Animal studies (e.g., shedding)
4) Transmissibility – a proxy of which is 'duration and amount of shedding'

Data from human studies (if available) should be included when performing the risk assessments of such strains.

B. Proposed use of the novel poliovirus strains

The impact of proposed use of these novel and related poliovirus strains on the containment requirements must be considered - any risk assessment of novel poliovirus strains must include an assessment of the risk associated with the intended use of the strains.

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Containment requirements of nOPV2 strains after the complete review of data from phase 1 clinical trials conducted in Belgium conducted under contained conditions

Summary of CAG TC3 discussions and conclusions:

1. Sufficient information has been provided to conclude that both nOPV2 candidate vaccines could be considered for use, according to the specific terms of usage already provided, outside the containment requirements of GAPIII (e.g., clinical trials, outbreak response, stockpile)
2. One of the safety issues that must also be considered in the risk assessment of novel poliovirus strains is transmissibility of which 'duration and amount of shedding' is a proxy indicator.
3. The CAG agreed with the conclusions of the ESG with the prospect of adding environmental monitoring for polioviruses to the usage requirements to monitor duration and amount of shedding (e.g., around the nOPV2 phase 2 clinical trial sites) in countries performing these trials. A real-time reverse transcriptase polymerase chain reaction (RT-rtPCR) method to detect and differentiate between Sabin2 and the two nOPV2 candidate vaccines is available[2].
4. Based on the existing data, the number of trials subjects and the study design (deliberate release setting), the CAG recommends that:
   a) Countries performing these trials should consider the implementation of the following, whenever and whichever appropriate, in their trials: environmental monitoring for polioviruses around the trial sites, around trial subjects continuing to shed virus after the end of the trial period and monitoring of their close and family contacts. These should take into consideration the poliovirus reproductive rate (R_0) [which depends on factors such as population density, sanitation and hygiene conditions (population, environment, sewage systems and treatment)] and relevant factors (e.g., study population, number of subjects, etc):
      i. In countries with presumed low R_0, environmental monitoring throughout and after the trial may not be necessary. However, mechanisms should be put in place to identify and follow up trial subjects continuing to shed virus after the end of the trial period. Monitoring of close and family contacts of trial subjects should also be included in the trial.
      ii. In countries with presumed higher R_0, environmental monitoring for polioviruses around the trial sites may be necessary. If needed, mechanisms to identify and follow up trial subjects continuing to shed virus after the end of the trial period and their close contacts should be included in the trial.
   b) Appropriate national authorities [e.g., National Authority for Containment (NAC) or Ministry of Health] in countries of concern should ensure that their National Action Plan to Sustain Polio-Free Status as requested by their Regional Certification Commission (RCC) for the Eradication of Poliomyelitis is up-to-date.
   c) Since nOPV2 is considered poliovirus infectious materials by definition, they must be included in the inventories performed in Phase I (Preparation for PV2 containment phase) of GAPIII. The national authorities in countries (i.e., NAC or MOH) should inform their National Poliovirus Containment Coordinator (NPCC) or a similar body and the National Certification Commission (NCC) for the Eradication of Poliomyelitis to include these in their annual reports to the RCC.

[2] European Commission, GMO register, Deliberate release into the environment of other than plants GMOs for any other purposes than placing on the market (experimental releases), B/BE/18/BVW2 (A Phase 2, double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of two novel live attenuated serotype 2 oral poliovirus vaccines candidates, in healthy adults and adolescents previously vaccinated with oral polio vaccine (OPV) or inactivated polio vaccine (IPV), compared with historical controls given Sabin OPV2 or placebo). Available at: http://gmoinfo.jrc.ec.europa.eu/gmo_report.aspx?CurNot=B/BE/18/BVW2

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Next steps for nOPV2:

1. Two candidate strains [nOPV2 candidate 1 (S2/cre5/S15domV/rec1/hifi3) and nOPV2 candidate 2 (S2/S15domV/CpG40)] have already been tested for immunogenicity in a clinical phase I trial conducted in Belgium[2] under contained conditions. Of concern to the ESG is that some of the subjects continued to shed vaccine virus after 28 days, including for some days after the trial ended. Although these subjects continued to be monitored after the end of the trial period, no environmental monitoring for polioviruses was conducted. Study subjects in the trial were adults already immune to poliovirus type 2 by inactivated polio vaccine (IPV).
2. A clinical phase 2, double-blind, randomized, placebo-controlled, multi-centre study trial of the nOPV2 candidate vaccines is currently being deliberated jointly by the relevant authorities including the NAC in the country that received the trial application. This trial will evaluate the safety and immunogenicity of both candidate vaccines in a study population of ~ 330 OPV- and IPV-only primed adults and adolescents. The study is expected to last several months between Q4/2018 and Q1/2019 and will be performed under deliberate release conditions.
3. Another clinical phase 2 trial application, for a single center, age de-escalation, partly-blinded, randomized study involving a study population of ~ 700 children age 1-5-year old and 6-weeks old infants, is under review by another country. This study will also be performed under deliberate release procedure and is expected to last approximately 12 months.

The nOPV2 strain is intended for use as a safer alternative to mOPV2 vaccine for outbreak response. The primary endpoint of these Phase 2 trials concerns immunogenicity; the secondary endpoint concerns virus shedding. Population sizes selected for the trial are based primarily on meeting licencing requirements.

The discussions and deliberations carried out when evaluating the trial applications should involve the NACs or another authority e.g., MOH in addition to all other relevant institutions or committees e.g., National Regulatory Authority (NRA), relevant ministries, professional bodies of the related disciplines [e.g., biosafety, genetically-modified organisms (GMO)], etc.

CAG expressed the need to learn as much as possible about these strains, in addition to immunogenicity and virus shedding, while the opportunities present themselves. Environmental distribution and evidence for transmission to contacts and the wider community will provide valuable information against which an assessment of any future candidate vaccine strain can be made.

Containment requirements of S19 -poliovirus type 2 strains

Summary of CAG TC3 discussions and conclusions:

1. The CAG agreed with the conclusions of the ESG. Based on the available published evidence that S19 has a single mechanism for attenuation and is unlikely to infect humans at a biological temperature based on data from non-human primate studies, CAG concluded that the strain (S19/S2P1/N18S and S19/MEF1PI/N18S[3,4]) can be used outside of the containment requirements of GAPIII for purposes stipulated in the submissions made, e.g., IPV production, rat neutralization

[3] Knowlson S, Burlison J, Giles E, Fox H, Macadam A J, and Minor PD. New Strains Intended for the Production of Inactivated Polio Vaccine at Low-Containment After Eradication. PLoS Pathog. 2015; 11(12): e1005316. doi: 10.1371/journal.ppat.1005316

[4] Netherlands Commission on Genetic Modification (COGEM), Advisory Report: Activities with genetically-modified polioviruses (CGM/171220-01). Available at: https://www.cogem.net/showdownload.cfm?objectId=BC73A5D7-D984-AE6C-D09D1FB5A26D53A8&objectType=mark.hive.contentobjects.download.pdf

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

2. S19 strains are currently being used in some countries as seed stock to produce IPV with the ultimate goal of using the strains for technology transfer of vaccine manufacturing capacity to other countries. WHO Secretariat has contacted the relevant authorities in these countries who provided the approvals and attempted to put them in contact with the NAC, some countries had not been informed of the approval given for use of S19 outside of GAPIII containment.
3. Concerns have previously been raised that although *in vitro* replication of S19 at 37°C is significantly reduced compared to replication at 33°C, human infection through the nasal passages, which may be several degrees lower than 37°C cannot be completely ruled out. At this point, however, it should be regarded as a hypothetical concern and it remains very unlikely that S19 would be capable of infecting humans.
4. Based on the existing data, the CAG recommends that:
    a. The relevant NAC or another authority, e.g., MOH, should ensure that the facility has in place an emergency and contingency plan that is linked to the national response plans for responding to the potential release or exposure to poliovirus
    b. The CAG considered at this point it was not necessary to recommend the companies conduct monitoring of their production staff for evidence of infection with S19.
    c. Since S19-poliovirus type 2 strains contains poliovirus type 2 capsid sequence it meets the definition of poliovirus infectious materials and therefore must be included in the inventory performed in Phase I (preparation for PV2 containment) of GAPIII. The national authorities in countries (i.e., NAC or MOH) should inform their National Poliovirus Containment Coordinator (NPCCs) or a similar body and the National Certification Commission (NCC) for the Eradication of Poliomyelitis to include these in their annual reports to the RCC.

Responses from the Secretariat:

a) WHO will not issue an exemption as this should be a collective national responsibility i.e., the relevant NAC in collaboration with other relevant agencies or regulatory bodies;
b) The CAG should be informed accordingly (containment@who.int)[5]

These recommendations issued by the CAG are conditional approval by ongoing use and are therefore not covered by Annex 2 (facilities retaining WPV/VDPV) or Annex 3 (facilities retaining OPV/Sabin infectious materials) as described in GAPIII.

[5] Submissions on issues for the consideration of the Containment Advisory Group can be made using the CAG submission form (available at: http://polioeradication.org/wp-content/uploads/2018/02/RequestCAG-2018-02.docx), and should be emailed to containment@who.int.

Annex 1. ESG conclusions for CAG Considerations/Decisions

Based on the data made available to the ESG on nOPV2 and S19-poliovirus type 2 strains and according to the specific terms of usage provided, the ESG concludes:

1. Genetic stability of attenuation of novel poliovirus strain is a critical factor to be considered. Other factors that are important, but less clear and of relative importance are:
    i. absolute attenuation relative to Sabin strain
    ii. infectivity
    iii. shedding infectivity
    iv. theoretical pathways to reversion.

    ∴ Are these criteria adequate and sufficient for present and future strain evaluation? [ESG recommendation – Yes]

2. Is the evidence sufficient to establish these strains as 'safer'?
    i. nOPV2 [ESG – Yes]
    ii. S19 strains [ESG – Yes]

3. Impact of proposed use on containment requirements. Should be considered? [ESG - Yes]
    i. nOPV2 – vaccine, outbreak response, stockpile (open use – no containment); Clinical trials in Belgium and Panama 2018/2019
    ii. S19-poliovirus type 2 strains – IPV seed strain (facility only use); e.g., technology transfer