RAG Risk Assessment Group

# PRIMARY RISK ASSESSMENT

## Poliovaccin UAM4a Study

| Date of the signal | Date of the RA | Signal provider | Experts consultation | Method |
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| 07/09/2017 | 08/09/2017 | SBB unit, WIV-ISP | **Permanent experts:**<br>Dr Daniel Reynders (FOD), Romain Mahieu (COCOM-GGC), Dr Carole Schirvel (AViQ), Mme Mireille Tomas (DG), Dr Sophie Quoilin (WIV-ISP), Dr Geert Top (AZG).<br>**Specific experts :**<br>M. Nicolas Willemarck (SBB), Dr Pierre Van Damme (UA), Dr Ilse De Coster (UA), Dr Philippe De Smedt (UA), Dr Charlotte Martin, (UMC St Pierre), Dr Steven Callens (UGent), Dr Béatrice Swennnen (PROVAC), Dr Elizaveta Padalko (UGent), Dr Marc Van Ranst (NRC polio, KUL), Dr D. Hue (FAGG), Dr Anne Leenaerts (FAGG), Dr Luc Tsashoua (SPF SP), M. Gert-Jan Sterck (Cabinet M. De Block), Dr Martine Sabbe (WIV), Dr Elise Mendes da Costa (WIV) | Urgent meeting |
| Date of update | Closing date | | | |
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| **Signal** | On the 7th September 2017, the service SBB (Biosafety and Biotechnology Unit, WIV-ISP) has informed the secretariat of the polio committee (WIV-ISP, service EID) by telephone of the observations made during the U4M4a study.<br><br>The U4M4a study is a phase 1 monocentric blinded study carried out by the Centrum voor de Evaluatie van Vaccinaties (University Antwerp). The primary objectives of the study are to assess for 2 candidate vaccines the general safety and the viral shedding. Secondary objectives of the study are to evaluate the immunogenicity and to examine the neurovirulence and the genetic sequence of the shed virus. This study is carried out in contained conditions (modular contained facility – study location: University Antwerp) among healthy adults 18-50 yr old previously primed only with inactivate polio vaccine (IPV). This study consists of sequential cohorts of 15 volunteers randomly allocated to the nOPV2 Candidate 1 or the nOPV2 Candidate 2. Shedding is monitored via daily stool sampling and nasopharyngeal sampling. Among the 30 participants, 24 live in the Netherlands and 6 in Belgium. Participants to the study are held in containment (quarantine) during 28 days, or until all subjects are PCR-negative for 3 consecutive stool samples. If shedding continues after 28 days, volunteers can leave the site of the study while applying post-discharge precautions (contact precautions, chemical toilet use, stool samples collection … and not leaving Belgium and not travel towards the Netherlands and towards endemic countries). For reminder, the participation to any clinical trial is voluntary and each person has the right according to ICH-GCP to leave the trial if wanted.<br><br>Sample analyses are performed by the CDC (Atlanta). In consequence, there is a delay of 3-4 days between the sampling and the results.<br><br>The full containment phase for the second cohort ended on August 22 (day 28) with approximately half of the subjects negative for shedding for at least 3 consecutive stool samples. As an additional precaution, those who were still shedding were instructed to use chemical toilets for stool collection and were housed at a hotel facility in Belgium or in private accommodations in Belgium while further testing of stool samples continued.<br><br>- Among those who are living in the Netherlands, one subject, who was still a shedder by trial definition, went back to the Netherlands from the hotel facility on September 2nd, but agreed to adhere to the recommendations of using chemical toilets, daily stool collection for testing and measures. Additional testing of samples from this subject indicated that s/he was negative for shedding by the time of return to the Netherlands.<br><br>-Among the two subjects identified as re-shedders one was considered non-shedder on day 28 and went to the Netherlands, the other one was still shedding and stayed at the hotel facility in Antwerp for a few days until he also delivered three negative samples en went back to the Netherlands and subsequently had a later sample test positive (about four days delay between sampling and results). These subjects have been contacted and have agreed to use provided chemical toilets for stool collection, and to provide stools for further testing. For these subjects, shedding has been at very low titers. |

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| | The team carrying out the study anticipated that one volunteer with shedders-status would decide to go to the Netherlands and informed the SBB on 30/08. Observations of re-shedding were communicated on 31/8/17. While considering there was a containment rupture, the SBB has taken contact with the Flemish Government (31/08/17 and 4/9/17) and has taken contact with the RIVM (GMO section). A risk analysis was performed by the SBB (WIV-ISP) prior to the beginning of the trial and concluded that the 2 candidates vaccine are non-pathogenic genetically modified micro-organisms, and that the genetic modification aimed at increasing the genetic stability of the strain compared to the parental strains so as to lower the probability of reversion (compared to the Sabin OPV2 strain). The RIVM does not share this analysis and estimates that the genetically modified strain used in the candidates vaccines can be considered as pathogenic.<br><br>Research team leading the trial study (including CDC-Atlanta) is also assessing the risk. It currently considers the risk as low as the concentrations are at the detection limit. For concluding their risk assessment, they wait the results of the Whole Genome Sequencing analysis. |

| **Description** | | **Score** | **Description / arguments** |
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| 1 | Cause known? | Yes | Poliovirus is well known but this is not the case for the current genetically modified vaccine candidate. |
| 2 | Unexpected/unusual | Unexpected | Shedding following oral polio vaccine administration is a known phenomenon, and varies depending on age and prior vaccination status, among other factors. It is not unusual to observe shedding 2-3 months following challenge, although the mean duration of shedding has typically been documented as until 3-4 weeks (what as used for the duration of the containment). Although some subjects are still shedding, the titres are declining as expected. Intermittent pattern of viral shedding has been observed with polioviruses in the past, and that is why the requirement of having 3 consecutive negative samples is there in the protocol for a subject to be considered negative for shedding. Although this is not completely unusual, re-shedding after 3 or more negative samples was unexpected. |
| 3 | Severity | Low | The vaccine strains used in the trial are attenuated type 2 poliovirus. Type 2 poliovirus is known to be more virulent with a higher reversion capacity. The reversion capacity of these strains in human is not known (first human assay). However, cellular passage studies showed that the current vaccine candidates have a lower risk of reversion compared to the current vaccine strain. The results of Whole Genome Sequencing by CDC are expected in October/November. |
| 4 | Dissemination (Low/Medium/High) | Very low | Very low as the concentration of viral material is sharply decreasing after vaccination and as the value among the two re-shedders are around the detection limit. Also the shedding was proven by PCR only so there is actually no direct proof of viable virus in the stool. |

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| | | | The 2 re-shedders are still applying post-discharge precautions.<br>But the possibility of re-shedding for participants who were considered non-shedders is currently unknown. |
| 5 | Risk of (inter)national spread | | Netherlands: at possible higher risk because of Bible belt (area with lower vaccination coverage) and because the Netherlands has never been exposed to OPV, only IPV since '60; what gives only systemic immunity protecting from polio disease but not from polio infection and dissemination.<br>Very low in Belgium thanks to high vaccine coverage (98,2% polio 3, 93% polio 4, national average in 2016). And population exposed to OPV until 2001 (year of switch to IPV) with mucosal and systemic immunity to polio in an important part of population. |
| **Preparedness and response** | | | |
| 6 | Preparedness | | Study protocol validated by WHO, Ethic Committee and Biosecurity Committee. The Biosecurity committee have accepted a 'contained use only' dossier based on an 'expected' shedding period not longer than of 28 days. |
| 7 | Specific control measures (surveillance, control, communication) | | Containment during the study and specific precautions in place in case of shedding. |
| **Public health impact** | | | |
| A | Public health impact in Belgium (Low/Medium/high) | Low | Risk in Belgium considered very low because of high vaccination coverage and since re-shedding occurs at level of detection limit but<br>Considering the poliomyelitis eradication goal of WHO,<br>Considering that the re-shedding after 3 consecutive negative stool samples is unexpected,<br>Considering uncertainties about the reversion capacity of the genetically modified virus,<br>additional investigation should be conducted in the context of the clinical trial. |
| B | Recommendations (surveillance, control, communication) | | **Proposed surveillance measures :**<br>1. Culture of the stool samples from the 2 participants who are re- shedding viral material,<br>2. To contact the other 28 participants and ask them to provide 3 consecutive control stool |

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| | | | samples on which a PCR will be performed. The sampling will be repeated after 14 days if the PCR come back positive.<br><br>These studies will be performed as an addition to the trial as the protocol does not allow disclosure of the identity of participants and in order to ensure the comparability of the results (PCR will be performed by same lab – CDC).<br><br>**Control :**<br><br>The two participants still shedding must continue to apply post-discharged precautions (e.g.: use chemical toilets, no travel in endemic countries, contact with immune-compromised people…) until they become negative.<br>The other participants will not have to apply these precautions unless the control stool specimens are negative in the follow up. If the specimens are positive then post-discharged precautions will be recommended, sampling will be recommended among households contacts of the participant and among at risk persons (e.g.: immune-compromised people, young children…) having been in closed contacts as well.<br><br>**Communication:**<br><br>The proposed measures will be transmitted and discussed with the RIVM.<br><br>WHO and Eradication Committee will be asked to evaluate if proposed measures are needed and if so, whether sufficient.<br><br>A common notification to the IHR, Eradication Committee and EWRS will be done by the Belgian and Dutch NFP's.<br><br>As a technical expert for Department Omgeving, the SBB will ensure further follow-up for the competent authority (Departement Omgeving) with regard this 'contained use' approval.<br><br>As more life vaccination trials (e.g. viral vectors vaccines) will be conducted in future, a bio-ethics discussion is needed on the voluntary nature of leaving a trial when it could have potential negative public health effects: What if patients refuse quarantine? Or refuse all measures proposed? Can a higher authority decide to forcefully hold a patient? |
| C | Actions | | Belgian NFP will take contact with Dutch NFP to |

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| | | | organise on Monday 11th September a teleconference.<br>SBB (WIV-ISP) informs Departement Omgeving (Flemish Government).<br>NFP's make a common notification to IHR, Eradication Committee and EWRS with approval on proposed measures. |

## REFERENCES

**Background information**

Sabin 2 vaccine component has been withdrawn from routine use globally from April 2016 per SAGE recommendations. Following this OPV2 cessation, stockpiles of mOPV2 are being maintained for use in outbreak response. However, there is a risk of cVDPV2 from Sabin type 2 in settings of low population immunity. Research has been ongoing to develop vaccines that are genetically more stable than the currently available Sabin 2 containing OPVs. Two nOPV2 vaccine candidates have been developed as attenuated serotype 2 polioviruses derived from a modified Sabin 2 infectious cDNA clone. nOPV2 Candidate 1 and nOPV2 Candidate 2 were generated by modifying the Sabin-2 RNA sequence to improve phenotypic stability and make the strains less prone to reversion to virulence.

Eurosurveillance, Volume 22, Issue 21, 25 May 2017. Rapid communication. RESPONSE TO A WILD POLIOVIRUS TYPE 2 (WPV2)-SHEDDING EVENT FOLLOWING ACCIDENTAL EXPOSURE TO WPV2, THE NETHERLANDS, APRIL 2017. E Duizer , WL Ruijs , CP van der Weijden , A Timen.

**Annexes:**

- Summary Novel OPV-2 Development: Update from FIH Clinical Trial ("M4-a") under Containment (New OPV2_M4a_090617_vf.pdf)
- Presentation Pierre Van Damme - Infosessie poliovaccinstudie: M4a (UAM4a infoslides_final FOD 2017.pdf)