

Summary Note for Record

Meeting of the GACVS (Global Advisory Committee on Vaccine Safety) Subcommittee on Novel Oral Polio Vaccine Type 2 (nOPV2) Safety

July 20, 2023

The GACVS sub-committee on nOPV2 safety met virtually on July 20, 2023 to review the progress of nOPV2 roll-out and evaluate the safety profile of the vaccine using updated safety data from campaigns through May 31, 2023. The committee additionally reviewed and provided guidance for planning of transition of safety monitoring activities post pre-qualification of nOPV2.

The committee concluded that, based on the available data, **there was no evidence of any geographical or temporal clustering of AESI reports that would indicate a safety concern, and no other obvious red flags or safety concerns.** Further details from the discussions, including the full set of committee recommendations, follow.

nOPV2 roll-out, field effectiveness and clinical study updates

The GPEI nOPV working group presented an update on the progress of nOPV2 roll-out along with results from field effectiveness evaluations and clinical studies on the safety, and genetic stability of the vaccine:

- Between March 2021 and July 2023, 670 million doses of nOPV2 were administered across more than 130 campaigns in 31 countries. The overall impact of nOPV2 on cVDPV2 outbreaks is favorable, with nearly two-third of all outbreaks interrupted with 2 SIAs, in line with mOPV2 performance.
- An ongoing evaluation highlighted the field effectiveness of nOPV2 compared to mOPV2 for stopping outbreaks. While most countries required two or fewer campaigns to control outbreaks of circulating vaccine derived poliovirus type 2 (cVDPV2), few countries like Nigeria, Democratic Republic of Congo (DRC), and Niger needed additional campaigns regardless of the vaccine used, consistent with known variations in vaccine performance across geographies.
- Recent clinical studies have demonstrated the immunogenicity and safety of two-doses of nOPV2 administered in shorter, two-week interval is non-inferior to their administration over the standard four-week interval. The administration of the two doses over a one-week interval was found to be slightly lower in immunogenicity compared to the four-week interval. Based on these findings, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended the use of shorter interval campaigns for nOPV2, in select settings in its March 2023 meeting.

- In a study led by the US Centers for Disease Control and Prevention (CDC) the concomitant administration of nOPV2 with the bivalent oral polio vaccine (bOPV) did not pass non-inferiority for type 2 immunogenicity compared with nOPV2 alone. At the same time, field data from environmental surveillance did not show significant differences in virus isolation relative to timing of prior SIAs compared to mOPV2.
- Despite the large-scale rollout, less than 2% of all whole genome sequenced isolate reported as of March 31, 2023 showed evidence of losing key genetic modifications of nOPV2 due to recombination (vs. expected 75% for monovalent Oral Poliovirus Vaccine type 2). Currently, five cVDPV2 emergences have been detected with nOPV2 origin. Three of these five emergences appear to have stopped before generating more than 10 cases of acute flaccid paralysis (AFP).
- The prequalification (PQ) dossier for nOPV2 was submitted by Biofarma in March of this year as planned. PQ is targeted for end of 2023.

Genetic characterization update

The nOPV2 genetic characterization sub-group updated the committee on latest findings on the issue.

- Between March 2021 and May 2023, whole genome sequencing analysis of 1,261 isolates confirmed to be derived from nOPV2, from stools and environmental samples collected in 19 countries confirmed the enhanced genetic stability profile of nOPV2 relative to the Sabin OPV2 experience.
- With the exception of few recombinant nOPV2 isolates detailed below, none of the nOPV2 isolates sequenced in this period had reversions in the primary attenuation site of nOPV2 (domain V, nucleotide 529-596, in the 5' NCR). This is in contrast to Sabin OPV2, which reverts by mutations in this site in nearly all vaccinees within 14 days of vaccine administration.
- Mutations altering base pairing in RNA secondary structures in the 5' NCR region and VP1 reducing attenuation were observed in some nOPV2 isolates. However, few of the mutation combinations identified elsewhere in the genome of nOPV2 isolates would be predicted to cause the nOPV2 strain to approach the neurovirulence of the Sabin 2 poliovirus strain with a single A481G reversion in Domain V.
- There have been 14 nOPV2 isolates found with a double recombinant genomic structure. Such double recombination events resulted in the loss of all nOPV2 genetic modifications in these isolates, except for silent capsid genetic markers, and the expected loss of attenuation properties. Five cVDPV2 emergence groups derived from double-recombinant nOPV2 isolates have been identified.
- In addition to the above, two patients with primary immunodeficiency disorders (PID), without AFP were shown to excrete nOPV2 for long periods of time (at least 288 and 310 days). Despite the observed

long-term excretion, domain V was fully preserved with no mutations in this region in any of the isolates from these two PID patients.

Gambia safety study

The Medical Research Council Unit, The Gambia at the London School of Hygiene & Tropical Medicine (MRCG @ LSHTM), conducted a study on the tolerability, safety and systemic and mucosal immunogenicity of nOPV2 in a campaign in The Gambia. Key findings from the study were presented by the unit to the sub-committee.

- The campaign was conducted across 3 communities in The Gambia. Baseline data was obtained from over 5,500 participants, with approximately 90% of them receiving the first dose and 87% receiving the second dose. In total, about 80% of the participants received both doses of the vaccine.
- A significant proportion of the participants were one year old or younger, with an equal distribution of males and females, and the demographic distribution was similar to that of the communities involved. Approximately 6.7% of the participants were severely malnourished, and about 18% were either moderately or severely malnourished.
- The frequency of solicited systemic adverse events following immunization (AEFIs), two to seven days post each round of the vaccine did not increase compared to baseline and mostly consisted of mild conditions. Further, no Adverse Events of Special Interest (AESIs), or other AEFI were considered to be causally related to nOPV2 over the two campaign rounds.
- nOPV2 was well tolerated, with no safety signal being identified in the week following vaccination, in a cohort of over 5,000 under 5-year-olds in rural settings in The Gambia.
- Prior to vaccination, 67% of participants were seropositive for type 2. This increased to 88% after the first round and further to 97% after the second round of vaccination. For participants who were seronegative at baseline, the conversion rate was 70% after the first round and increased to 91% after two doses of the vaccine.
- The study demonstrated some evidence of heterotypic immune response to other serotypes (one and three) and induction of mucosal immunity.

nOPV2 Safety Data Update

The nOPV2 safety sub-group provided a summary of new and updated data reported during the period between November 1, 2022 and May 31, 2023. During this period, 31 campaigns were held in 17 countries.

- The cumulative period of all safety data collected from nOPV2 campaigns ranged from March 2021 to May 2023. During this period, 9,600 adverse events (AEs) were reported, 1,576 of which were serious and 6,431 non-serious – the remainder being of unknown seriousness.
- The majority of AEs post-nOPV2 remain signs and symptoms associated with vaccine reactogenicity and tolerability, such as pyrexia, diarrhoea and vomiting – the 3 events accounting for 55% of all recorded AEs. The next most common AE recorded was cough, representing 8% of all AEs reported.
- 445 adverse events of special interest (AESIs) were reported through all surveillance systems. Approximately 58% of AESIs received a causality grading (A1 to C), 2% were ineligible or unclassifiable, and 40% have not been assessed for causality or data for causality assessment has not been shared.
- To date, there were 9 reports of suspected cases of Vaccine-Associated Paralytic Poliomyelitis (VAPP) in total, reported from Cameroon (4) and Nigeria (5). National Expert Committee (NEC) assessments are available for 5 of these cases from Nigeria, which were all classified as A1 – causally related to nOPV2. These 5 cases showed residual paralysis at the 60-day follow up. Genetic sequencing was available for all 5 cases, indicating a low level of concern for mutation per the Genetic Characterization classification scheme. The remaining 4 cases from Cameroon have not yet been classified yet by the NEC due to paucity of information. The VAPP rate for nOPV2 to date remains lower than that of mOPV2.
- To date, considering data from all 544,120,539 doses administered within the observation window for this report, 66 SAEs (from both AEFI and AESI surveillance) have been assessed as causally related to nOPV2 (A1 classification) by all National Expert Committees (NECs), including 2 new cases of febrile convulsion and myelitis, and one case each of encephalitis, acute gastroenteritis and Guillain-Barré Syndrome.
- Five cVDPV2 emergences have been detected that are derived from nOPV2 to-date in Nigeria, CAR, and DRC (with detections in Burundi and Zambia). These emergences have been collectively linked to a total of 39 cases of acute flaccid paralysis (AFP) to date. This remains significantly below what would have been expected with mOPV2 use at the same scale over the same period of time.
- Data completeness and timeliness continues to be a challenge:
 - AEFI surveillance data available for all campaigns only across 12/28 countries
 - Causality assessment data incomplete/pending from 16/28 countries
 - Final diagnosis not available for 45% SAEs
 - Line-listing not submitted for 392 AEFIs from 8 countries
- Limited capacity for surveillance, case ascertainment and classification continue to hinder nOPV2 safety monitoring

- 2 countries reported no AEFIs, and one country submitted only pooled AEFI reports for all vaccines combined
- 6 countries reported no AESIs
- 25/28 countries continue to demonstrate functional AFP surveillance, forming a consistent backbone to the overall safety surveillance strategy
- 25/28 countries continue to implement and report on AEFI surveillance
- Observed AESI rates were below or within background rates from literature
- The number of serious adverse events found to be related to nOPV2, causally (A1) or temporally (B1) – as assessed by local NECs, continues to be low at a rate of less than 1 event per 5 million doses
- The rate of VAPP from nOPV2 surveillance continues to be lower than the rate that might be expected with the oral Sabin vaccine; 0.0009 / 100,000 doses for nOPV2 vs 0.025 – 0.4 / 100,000 doses for Sabin OPV
- Acknowledging the caveats of safety data limitations, there continues to be no evidence of any clusters or patterns of AE reports, either temporally or geographically, that would give rise to any unexpected safety concerns

Update on action taken to implement previous recommendations of the sub-committee

The safety sub-group updated the sub-committee about actions undertaken in response to previous recommendations of the sub-committee, including the following actions:

- Based on recommendations from the sub-committee in the previous meeting, an initial draft of an ongoing temporal study was shared with the sub-committee for their feedback. The analysis aimed to delineate the median time to onset for all AEFIs with a valid or final diagnosis reported post nOPV2 vaccination between March 2021- May 2023.
 - Over 1,488 AEFIs with valid or final diagnosis were reviewed, of which 10% had to be excluded due to invalid or missing dates of vaccination. Median onset was calculated for a total of 1,351 AEFIs.
 - Median onset ranged from 1-2 days for events like anaphylaxis and seizure to 24 days for VAPP and 48 days for acute disseminated encephalomyelitis.
 - The sub-group plans to undertake modeling to address missingness of vaccination dates, and conduct sensitivity analyses for examining the impact on median time to onset by dose and levels of diagnostic certainty.
- A detailed literature review was undertaken to update background rates for AESIs- by country and region where available. The most common sources included nationally representative surveys and GBD

estimates. There was a paucity of literature on geography and age specific background rates for many of the AESIs. The safety sub-group team continues to refine reference values for AESIs based on latest available literature.

- The safety sub-group reviewed and identified cases with missing clinical information, and potentially misclassified cases from the safety database. A detailed list of such cases, along with the rationale for their inclusion in the list was shared via the regional WHO office for further re-evaluation and follow-up by respective NECs. Updated causality assessment information was received from one country before, and from six countries after the data lock-point.
- To improve timeliness and completeness of nOPV2 safety data, a data-sharing escalation plan was prepared and implemented with support of respective WHO regional offices. The plan will be further refined based on experience from the current round of data review.
- To continue to strengthen capacity for causality assessment, safety refresher trainings were conducted in 9 countries; and regular follow-up with national nOPV2 safety focal points is being conducted to provide support and ensure timely data sharing from countries implementing nOPV2 campaigns.

Planning for transition of safety surveillance activities post nOPV2 prequalification (PQ)

The GPEI nOPV working group updated the sub-committee about the targeted pre-qualification of the vaccine by end of 2023, and subsequent plans for transition of the safety surveillance activities.

- nOPV2 has been used under an emergency listing since March 2021. So far, about 670 million doses have been administered, and an additional 250 to 350 million doses are expected to be given this year.
- nOPV2 is currently undergoing regulatory review for full licensure in Indonesia and pre-qualification by WHO. This review process is aiming for completion by the end of 2023.
- If and once nOPV2 is fully licensed and pre-qualified, there would be a shift in the processes and procedures around its use. The enhanced safety monitoring that is currently in place would end, and nOPV2 would be rolled out and used like other fully licensed and pre-qualified vaccines.
- The GPEI nOPV Working Group, which was established to coordinate the rollout of nOPV2 under EUL, will close. A short time frame will be available to wrap up and transition activities of the working group, including its safety sub-group post PQ.
- It is proposed that enhanced safety surveillance undertaken for the nOPV2 under the EUL will be transitioned to reflect routine safety surveillance practices for all other licensed and prequalified vaccines post PQ. The specific plan for each of the safety surveillance group's activity is provided below:

- **Monitoring of nOPV2 Campaigns:** The Safety Subgroup monitors ongoing nOPV2 campaigns to calculate rates of adverse events by doses, campaigns, and locations. This activity will be continued by the Outbreak Response and Preparedness Group (ORPG) within GPEI, which tracks doses administered globally.
 - **AFP Surveillance:** National AFP surveillance networks, which have demonstrated capacity in detecting, reporting, and investigating cases will continue to be the mainstay for nOPV2 safety monitoring. The working group proposed drafting standard operating procedures (SOPs) for enabling existing national AEFI committees to review AFP surveillance information in the context of nOPV2 vaccine safety monitoring. The working group highlighted the absence of standardized case definitions for conditions like VAPP, which impedes the collection of reliable and comparable information on these conditions across diverse geographies and clinical care settings.
 - **Integration into Reporting Systems:** Post PQ, efforts will be made to integrate nOPV2 safety monitoring into standard AEFI reporting procedures. The pharmacovigilance team will coordinate with WHO immunization, vaccines and biological (IVB) team to ensure nOPV2 is included in all AEFI reporting systems.
 - **Quarterly Review Mechanism:** There is a proposal to continue a quarterly review mechanism post pre-qualification for a limited transition period, where reports from countries will be monitored using existing portals (e.g., with Vigiflow) to track identify any emerging safety signals related to nOPV2.
 - **Guidance:** To support the transition, existing guidelines for safety monitoring of nOPV2 will be updated, and a guidance note will be prepared to ensure continued safety monitoring at the country-level.
- The group also proposed the development of two manuscripts in collaboration with the sub-committee members and nOPV2 implementing countries to characterize the safety profile of nOPV2 under EUL and to document the lessons learned from this unique multi-country pharmacovigilance initiative.
 - With the targeted pre-qualification of the vaccine in Q4 2023, the group sought feedback from the sub-committee regarding its eventual closure. Two options were presented to the sub-committee regarding its final meeting: (i) assuming a final campaign may be held in the week preceding PQ, and allocating a subsequent 24-25 weeks for the collection, investigation, review and analysis of its safety data, a final meeting of the sub-committee was proposed in July 2024; (ii) alternatively the final meeting may coincide with the PQ expected towards the end of 2023.

Discussion and key recommendations

- Overall, the sub-committee members appreciated the efforts undertaken to continuously improve the quality and completeness of nOPV2 safety data. It was highlighted, that by the time of its PQ, the safety of the vaccine would have been monitored across nearly a billion doses, making nOPV2 among the most rigorously evaluated vaccines prior to pre-qualification.
- The committee concluded that, based on the available data, there was no evidence of any geographical or temporal clustering of AESI reports that would indicate a safety concern, and no obvious red flags or safety concerns.
- Members expressed their concern regarding the volume of data presented and the paucity of time for the discussion. The safety sub-group suggested follow-up of any outstanding concerns over email, and reiterated their commitment to further refine the safety report and presentation in subsequent meetings.
- The sub-committee members expressed concern regarding the detection of 5 cVDPV2 emergences related to nOPV2, and the geographic clustering of these new emergences in few regions. The nOPV2 safety sub-group and working group members clarified that:
 - Findings from recent modeling estimates, suggest that ~57 cVDPV2 emergences would have been seeded if Sabin OPV2 was used at this scale instead of nOPV2, approximately 38 of which would have been detected by end Q2 2023 (as opposed to the 5 detected). This suggests that much of the emergence risk from earlier campaigns, conducted 1-2.5 years ago, may have already "expired" or been resolved, as there has been enough time to detect if seeding of cVDPV2 occurred.
 - The issue of risk of emergence is closely linked with the setting, and so far, the per-dose risk of new emergences appears to be higher following nOPV2 use in DRC and CAR (and neighboring areas) relative to the observations in other countries. Several factors warrant further evaluation, including relatively higher prevalence of non-polio enteroviruses suitable for recombination with nOPV2. On the other hand, a traditionally high-risk area such as Nigeria reported only one emergence (that did not appear to sustain) with massive scale of nOPV2 use.
 - Genetic reversion and cVDPV2 emergences are monitored closely and regularly reported on by the Genetic Characterization subgroup, where additional data on these emergences can be found.
 - cVDPV2 emergences derived from nOPV2 may be observed in under-immunized areas, especially with the massive scale of nOPV2 use and the challenges in implementing high quality outbreak response that reaches all children. Implementation of high quality and

- coverage nOPV2 campaigns and close monitoring of genetic mutations in nOPV2 are critical for mitigating the risk of new emergences.
- Sub-committee members sought to understand the overall utility and effectiveness of environmental surveillance for identifying genetic changes and cVDPV2 emergences. The nOPV working group acknowledged the importance of both environmental and AFP surveillance in monitoring poliovirus variants. As new emergences are linked to sub-optimal immunization coverage areas, environmental surveillance significantly complements AFP surveillance, providing additional insights into poliovirus prevalence, but its effectiveness may vary depending on implementation and operational factors.
 - The sub-committee recommended that the literature review undertaken for identifying comparable background rates, and median time to onset of events is continued. They also suggested referencing reported rates of AEFI from other comparable vaccine roll-outs, including from the meningococcal A conjugate vaccines, per availability.
 - The sub-committee members highlighted the importance of conducting temporal analyses as a means to identify emerging safety signals and made several recommendations for improving the draft results presented, including:
 - Addressing the 10% data with missing dates through data cleaning and modeling exercises
 - Conducting a sensitivity analysis restricted to events which occur within a biologically plausible risk-window based on literature review, particularly in the context of neurological AEFIs.
 - Analyzing the median time to onset for AEFIs by levels of diagnostic certainty, dose and causality classification.
 - Sub-committee members expressed concern about the lag period between reporting of AEFIs and their subsequent causality assessment by NECs. Causality assessments continue to be pending from many countries. The sub-committee recommended that the pending data escalation request plan is further improved to ensure availability of more complete data for subsequent meetings.
 - The sub-committee sought clarification regarding the reporting of malaria cases as AEFIs, and their classification as product related reactions (A1) in certain instances. Colleagues from regional office clarified that these cases were likely initially reported on the basis of common signs and symptoms such as pyrexia and chills and were only diagnosed as malaria following detailed investigation undertaken for AEFIs.
 - The efforts undertaken to strengthen the quality of causality assessment classification were appreciated. The sub-committee members recommended that additional trainings are conducted, prioritizing

countries with pending data, and those with poor timeliness and completeness of the submitted nOPV2 safety data.

- In regard to the plan for transition of safety surveillance activities as nOPV2 exits its EUL use phase, the sub-committee members made the following observations:
 - They requested for more time to deliberate over the details of the proposed transition of safety surveillance activities. In particular, members wanted to ensure there would be continued tracking of genetic variants of the polio vaccine post PQ. Due to paucity of time, the sub-committee secretariat suggested follow-up over email to further outline to the committee members how GPEI will continue to implement this tracking during the PQ period.
 - They reiterated the importance developing manuscripts for wider public dissemination of the key findings and lessons from the safety surveillance of nOPV2 under the EUL period, and agreed to contribute to the drafts of the manuscripts. The safety sub-group has been tasked with development of timelines for review and finalization of the manuscripts.
 - The members additionally recommended the development of a comprehensive workbook to aid future vaccine roll-outs under EUL.
 - They agreed that the sub-committee will continue functioning until it can conduct a final comprehensive review of data from all campaigns conducted during the EUL period. Thus, the final meeting for the sub-committee will tentatively take place in July 2024, assuming nOPV2 is pre-qualified in December 2023.

Members from the nOPV2 secretariat thanked the committee for their valuable insights. The next meeting of the sub-committee will be scheduled in Q1 2024.