

Summary Note for Record

Meeting of the GACVS (Global Advisory Committee on Vaccine Safety) Sub-committee on Novel Oral Polio Vaccine Type 2 (nOPV2) Safety- January 23, 2024

The GACVS sub-committee on nOPV2 safety met virtually on January 23, 2024 to review the progress of nOPV2 roll-out and evaluate the safety profile of the vaccine using updated safety data from campaigns up till November 15, 2024.

Update on nOPV2 roll-out and prequalification:

The nOPV working group presented an update on the progress of nOPV2 roll-out, WHO pre-qualification and performance of the vaccine

- nOPV2 was the first vaccine authorized under the Emergency Use Listing (EUL) procedure and received WHO prequalification on December 27, 2023. The prequalification process for a second supplier (Biological E) has been initiated and is expected in quarter 2-3, 2024, to supplement supply of the vaccine.
- During the EUL period between March 2021- December 2023, approximately 1 billion doses of the vaccine had been administered across 35 countries, becoming the vaccine of choice to respond to circulating vaccine derived poliovirus type 2 (cVDPV2) outbreaks in this time.
- Following prequalification, all countries need to issue new regulatory approvals to allow for use of the vaccine. nOPV2 monitoring, including surveillance and whole genome sequencing will be consistent with other OPVs.
- While activities such as readiness verification, and submission of safety monitoring data for review by the GACVS will no longer be required for vaccination campaigns conducted after prequalification; safety data for all campaigns conducted in 2023 must still be reviewed by GACVS nOPV2 sub-committee.
- The majority of isolates from the field showed no or minimal changes in the original nOPV2 vaccine sequence. Approximately 3% of whole genome sequenced isolates showed evidence of losing key genetic modifications of nOPV2 due to recombination, significantly lower than the expected 75% for mOPV2.
- 11 nOPV2 derived emergence groups have been detected so far in Democratic Republic of Congo (DRC), Central African Republic (CAR), Nigeria, Egypt, Botswana, Cameroon, and Zimbabwe. Most observed emergences have low case numbers, though the spread of two emergence groups underscores the importance of rapid response. Compared to Sabin OPV2, emergences derived from nOPV2 appear at a significantly reduced rate, based on a recent analysis of data through November 2023. Based on approximately 889 million doses used in the African region, 58.4 emergences would be expected to be reported by November 2023 if

nOPV2 seeded at the same rate as Sabin OPV2, compared with the 10 emergences reported from the African region (an 83% reduction)¹.

- Field data continues to suggest favourable safety, immunogenicity and enhanced genetic stability profile of nOPV2.

Genetic Characterization Update

The genetic characterization sub-group of the nOPV working group presented an update on the genetic analysis of available nOPV2 isolates.

- nOPV2 properties were fully characterized in the laboratory, demonstrating increased stability, similar immunogenicity, and yield compared to Sabin OPV2. Clinical trials further validated these findings. In the field, nOPV2 exhibited increased genetic stability, reducing the risk of causing disease or new outbreaks. Notably, nOPV2 was the first vaccine to transition from EUL authorized use to WHO pre-qualification, with close monitoring of genetic stability as a requirement.
- Most of the nearly 2000 nOPV2 isolates analysed through whole genome sequencing indicate no or minimal changes in genetic structure of nOPV2.
- The impact of different genetic changes on neurovirulence has been measured. The nOPV2 virus with multiple mutations remains more attenuated than the Sabin OPV2 virus with a single point mutation in domain V. Recombination events are observed for nOPV2, with single recombinants downstream of the cis-replicating element (CRE) having minimal effects on attenuation. Double recombinant nOPV2 viruses have been found having lost all attenuating modifications in nOPV2, making them phenotypically equivalent to wild-type polioviruses.
- 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.
- 11 cVDPV2 emergences have been detected that are derived from nOPV2 to-date in DRC, Burundi, Nigeria, CAR, Zambia, Cameroon, Chad, Zimbabwe, Botswana, Tanzania and Egypt.
- 10 of the 11 cVDPV2 emergence groups were found to be double recombinants between nOPV2 and species C enterovirus replacing all nOPV2 relevant genetic modifications. The double recombinants have lost all nOPV2 genetic modifications except for markers in virus

¹ Peak et al. 2023 “Monitoring the Risk of Type-2 Circulating Vaccine-Derived Poliovirus Emergence During Roll-Out of Type-2 Novel Oral Polio Vaccine”, 9th International Conference on Infectious Disease Dynamics: P2.029

protein 4 (VP4) and virus protein 2 (VP2) and are expected to have reverted to full neurovirulence.

- Two patients (non-AFP cases) with primary immunodeficiency (PID) excreted nOPV2 for long periods of time (338 and 593 days, respectively). 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.
- nOPV2 continues to demonstrate enhanced genetic stability and significantly lower likelihood of reversion to neurovirulence compared to Sabin OPV2.

nOPV2 field use safety data update

The nOPV2 safety sub-group presented updates from the fifth safety report, which covered field use safety data collected between March 10, 2021 to November 15, 2023 across 127 campaigns in 30 countries. Three countries (Rwanda, Mali and Kenya) which had additionally conducted campaigns during the evaluation period did not submit any safety data by the time of preparation of the report.

- **Data quality and completeness:**
 - Acute Flaccid Paralysis (AFP) surveillance was done in all countries, with 26 countries displaying functional AFP surveillance (i.e., more than 2 non-polio AFP cases per 100,000 children <15 years of age per year).
 - While all countries implemented passive surveillance of adverse events following immunization (AEFI), only 20 of 30 countries reported adverse events from this surveillance system. Of these, 11 countries reported more than 10 cases per 100,000 surviving children per year.
 - Active surveillance of adverse events of special interest (AESIs) was implemented in 18 out of 30 countries, although 4 countries discontinued AESI surveillance after having implemented it for earlier vaccination campaigns. Most countries reported less than 1 event per 100,000 vaccinations, with 5 countries not finding any potential AESIs or being unable to report data from that surveillance system.
 - Out of 30 countries, 23 have presented cases for causality assessment by National Expert Committees (NECs). Of the remainder, 3 countries did not report any serious events, while 4 countries reported serious events, but no NEC assessments were shared. NEC assessments have been received for nearly half of all serious events reported so far.
 - The date of vaccination was not reported for 9% of total adverse events reported. Around 40% of serious cases do not have a reported final diagnosis or valid diagnosis.
 - 27 out of 30 countries reported adverse events from at-least one surveillance system (including AEFI, AFP and AESI surveillance systems).

- AFP line lists received for 75%, AEFI and AESI line lists received for 71% and NEC line lists for 58% of all nOPV2 campaigns. This is a significant improvement from the 4th safety report, wherein AEFI line list data was only received from 40% of the conducted campaigns.
- Overall, 18,589 AEFIs (including serious and non-serious events) were reported across all countries throughout the entire safety surveillance period of nOPV2.
- To date, 5,164 events (including AESIs) have been recorded as serious by their latest assessment. Among the most reported SAEs were expected and common reactions to vaccinations, such as pyrexia (13%, n=697), diarrhoea (7%, n=362) and vomiting (4%, n=215).
- NEC assessments have been reported for 1,552 events, of which 1,455 received a graded causality assessment from grade A1 (causally related to nOPV2) to grade C (unrelated). The remaining events were deemed unclassifiable, invalid for assessment or downgraded to non-serious. The majority of cases, 87%, were assessed as not related (C) to nOPV2 or its administration.
- To date, 100 cases have been classified as either causally related (A1, n=67 cases) or temporally related (B1, n=33 cases) to nOPV2. The event most commonly assessed as related or temporally related is Guillain-Barré syndrome, with 14 assessments, followed by AFP, with 11 assessments. The number of SAEs 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 7 million doses**
- Overall, there have been **781 AESIs** reported by all countries. More than half of the AESIs (58%) are attributed to Nigeria, which is in accordance with their 55%-share of global vaccinations. Cumulative AESI reporting rates (as ascertained by the active AESI surveillance systems) are consistently lower, often by order of magnitude than the background incidence rates provided by literature.
- There have been 5 confirmed VAPP cases, all from Nigeria. Additionally, 4 cases of suspected VAPP were reported from Cameroon in previous safety reports, which have since been rejected by the NEC for poor data quality and were therefore not assessed for causality. Counting the 9 cases of VAPP, a conservative incidence rate for nOPV2, 0.001 / 100,000 doses, is lower compared to the Sabin vaccines. The VAPP reporting rates for the Sabin vaccine range from 0.03–0.14/100,000 doses for trivalent oral polio vaccine (tOPV) and 0.02/100,000 for bivalent oral polio vaccine (bOPV).
- A brief update regarding a cluster of AEFIs from Zambia was also presented to the sub-committee. The NEC reviewed clinical investigation reports from the AEFIs and assessed all the events to be coincidental in nature.

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

The following actions were undertaken to address previous recommendations from the sub-committee:

- Background rates and median time to onset of all AESIs were updated based on a comprehensive literature review.
- To continue capacity building efforts for improving quality and completeness of causality assessments conducted, a dedicated nOPV2 session was organized at the AFRO vaccine safety expert meeting in October 2023. The meeting was attended by NEC representatives from 45 countries in Africa, and facilitated by global and regional nOPV2 safety sub-group members in collaboration with the WHO pharmacovigilance team. Recommendations from previous GACVS nOPV2 sub-committee were reviewed collectively, and potential challenges in were discussed to facilitate completion of the pending causality assessments in relation to nOPV2.
- Brighton collaboration experts were consulted to develop and refine a working definition of VAPP as part of ongoing work towards strengthening detection and reporting VAPP cases.
- An updated temporal analysis was presented to delineate time to onset of AEFIs reported post nOPV2 using pre-defined risk windows based on prior published literature and biological plausibility. A sub-set analysis evaluating median time to onset of adverse events categorized by levels of diagnostic certainty was also presented.
- In its previous meeting, the sub-committee had discussed the need to address concerns about data availability during rollout of nOPV2 following pre-qualification to new countries. The sub-committee had suggested quarterly monitoring of Vigibase data for reports of nOPV2 related AEFIs for a limited time period post prequalification, however due to paucity of time this issue could not discussed in detail in the previous meeting. Feedback was sought from the sub-committee members regarding this outstanding issue. The safety sub-group highlighted concerns regarding the comparability of the Vigibase data with the safety surveillance data submitted directly by countries to WHO as part of the EUL requirements. The utility of continued monitoring of Vigibase data beyond the agreed timelines for the dissolution of the sub-committee was also discussed. A final meeting of the sub-committee will be tentatively scheduled in July 2024 to complete review of safety data for all nOPV2 campaigns conducted during the EUL period.
- The proposed timelines and plan for a manuscript on operational lessons learned during the multi-country pharmacovigilance initiative for monitoring safety of nOPV2 during the EUL period were presented to the sub-committee members.

Discussion and key recommendations:

- Sub-committee members expressed concern regarding the growing number of emergences and reiterated the importance of continued genetic surveillance in light of the anticipated wider use of the vaccine after pre-qualification.

- The sub-committee sought clarification regarding the risk-factors considered while modelling estimates of expected cVDPV2 emergences from Sabin versus novel OPV2 vaccines. The modelling considers factors such as the number of doses, the size of campaigns, the pre-campaign immunity level, and the time since immunization to estimate the occurrence of emergences. Further work is planned to assess how lower emergence rates can break the cycle of emergences.
- The subsequent discussion delved into the importance of population immunity status to OPV2 and the potential influence on the emergence of mutations. Findings from a recent publication highlighted risk factors such as pre-campaign immunity status and campaign characteristics for emergence². The modelling work considered these factors and includes sensitivity analyses. The containment measures required for nOPV2 were discussed, touching on the detection of double recombinants. The surveillance involves VP1 sequencing to identify outbreaks, and it is noted that outbreaks from nOPV2 have predominantly been double recombinants. The understanding is that the likelihood of nOPV2 causing outbreaks is much lower compared to Sabin OPV2 due to the specific genetic modifications in nOPV2 genome that necessitates specific pattern/sequence of recombination events with other enteroviruses to give rise to variants of public health concern.
- The nOPV working group members also clarified that once seeded, the trajectory and spread of cVDPV2 outbreaks from both nOPV2 and Sabin OPV are similar, reiterating the importance of, sustained high-quality surveillance, and rapid and high-quality response to contain all cVDPV2 outbreaks.
- The response for containment of nOPV2 related cVDPV2 outbreaks was also discussed in details. Sub-committee members sought clarification regarding potential use of the inactivated polio vaccine (IPV) and immunoglobulins for outbreak containment, and the latest guidance from SAGE were discussed in this regard³.
- The final question pertained to the role of immunity, specifically in malnourished children, regarding their susceptibility to recombination or prolonged excretion of the virus. The discussion highlighted the limitations in identifying the index child where recombination occurred, and the duration of virus excretion in malnourished children with studies on immunogenicity and immune response.

² Risk factors for the spread of vaccine-derived type 2 polioviruses after global withdrawal of trivalent oral poliovirus vaccine and the effects of outbreak responses with monovalent vaccine: a retrospective analysis of surveillance data for 51 countries in Africa. Cooper, Laura V et al. *The Lancet Infectious Diseases*, Volume 22, Issue 2, 284 - 294

³Meeting of the Strategic Advisory Group of Experts on Immunization, September 2023: conclusions and recommendations, *WER*: 47, 2023, 98, 599–620. Available at: <https://www.who.int/publications/i/item/WER-9847-599-620>

- While acknowledging the improvements in completion and quality of field use safety data, sub-committee members reiterated the need to further improve timeliness and completeness of nOPV2 safety data for campaigns under the EUL period, particularly in regards to the large number of campaigns with pending causality assessment reports for serious AEFIs.
 - The sub-committee has recommended that in its subsequent meeting all efforts need to be made to prioritize the assessment of causality of serious neurological AEFIs reported post nOPV2 campaigns during the EUL period, using a centralized and coordinated approach.
 - Representatives from regional and country vaccine pharmacovigilance teams highlighted the lack of resources for conducting relevant laboratory and field investigations, which are necessary for conducting causality assessments. They emphasized that the expert committee cannot perform assessments without minimum lab tests, and even if the technical materials are available, patients may lack resources to pay for the tests. The challenges with nOPV2 safety data completion highlight the need for continued strengthening and better resource allocation for vaccine pharmacovigilance in low- and middle-income countries.
 - The WHO pharmacovigilance team expressed their support for organizing regional and country-level meetings for completion of pending causality assessments for serious nOPV2 related AEFIs.
- In relation to the findings from the temporal analysis, the sub-committee made the following recommendations:
 - Revise the analysis with the wider risk-windows as the primary analysis, and the narrower risk-windows from literature as the secondary analysis.
 - In addition to box and whiskers plot presenting median time to onset for each event, it will be helpful to plot the distribution of time to onset of each event in number of days post vaccination.
 - To expand the risk-window for anaphylaxis beyond the current limit of 1 day post vaccination.
 - Include in the analytical dataset control conditions such as malaria to delineate reporting biases in the data, if any.
- To make an informed decision regarding the need for quarterly monitoring of nOPV2 related safety data in Vigibase (for a one-year period post prequalification), the sub-committee has requested that a comparative analysis regarding the quality and completeness of this database is presented in the next meeting.
- The sub-committee also recommended that in its final meeting (tentatively in July 2024), the following additional analyses are performed:

- Geographic, sex and age-distribution of AEs
- Assessment of feasibility of conducting hypothesis testing using case-only analytical designs (for e.g. self-controlled case series) for select neurological events.
- The sub-committee highlighted the need for continued efforts for strengthening vaccine pharmacovigilance in nOPV2 using countries, particularly in light of its wider used post prequalification. They emphasized the need for early detection of adverse events following immunization, and the allocation of adequate resources to prioritize completion of clinical investigations, thereby ensuring adequate data for evaluating causal association between vaccines and AEFIs.

The sub-committee members concluded that, with nearly 726 million doses of the nOPV2 being administered under EUL period with enhanced safety monitoring, the safety profile of this vaccine is well-defined. Acknowledging the caveats of safety data limitations, the sub-committee members reiterated that 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.