GACVS (Global Advisory Committee on Vaccine Safety) Sub-Committee on nOPV2 Safety
February 21, 2022 – Virtual Meeting
Summary Note for the Record

Summary of open meeting:

- The objectives of the meeting were: 1) to provide an update of the progress, and status, of safety surveillance of the novel oral poliovirus vaccine type 2 (nOPV2) and 2) for the sub-committee to provide an independent assessment of nOPV2 safety data generated from both initial and wider use countries.

- The nOPV Working Group presented an update on global nOPV2 usage. 240M doses of nOPV2 have been administered across 13 countries, with approximately 70% of nOPV2 doses administered in Nigeria. Outbreak data over the past six months show a decrease in cVDPV2 cases globally. However, there has been an increase in cVDPV2 cases in Nigeria in the same period. There have been delays in the timeline to move to full licensure and prequalification of nOPV2 that are due to delays in critical studies, notably the phase III study in the Gambia. The Working Group provided an update that readiness requirements for countries were simplified from 25 to 16 as part of the move to the wider use phase but noted that the safety requirements were not reduced. nOPV2 use under EUL is expected to continue through 2023.

- CDC presented an overview of a study in Uganda which focuses on the safety assessment of nOPV2 during a mass vaccination setting. The objective of this study is to identify and characterize safety events associated with nOPV2 following mass vaccination during EUL in Uganda with both passive and active surveillance. 1886 households were visited, and 1793 households consented. 2260 children were enrolled in cohort event monitoring. Preliminary data indicated that there were 31 serious adverse events, more than 50% of which were diagnosed as malaria. Further data and details are to be shared on the remaining serious adverse events.

- Safety data were presented from seven countries: Nigeria (88.1 million doses), Liberia (1.8 million doses), Benin (4.5 million doses), Congo (2.1 million doses), Tajikistan (2.5 million doses), Sierra Leone (3.8 million doses), and Niger (8.7 million doses). The data included adverse event following immunization (AEFI), adverse event of special interest (AESI) and acute flaccid paralysis (AFP) data.
    - The largest (and most complete) dataset for consideration was from Nigeria, from the surveillance period between March 2021 and February 2022, over which period 88.1 million doses were administered. In total, there were 586 AEFI and AESI cases reviewed by the national causality committee: 14 were classified as ineligible; 545 as inconsistent with causal association; 19 as indeterminate, 2 as unclassifiable; and 6 as consistent with causal association. The 6 cases considered causally related included one case of anaphylaxis, one meningoencephalitis and one allergic reaction – all are fully recovered – and three cases of suspected VAPP. The suspected VAPP cases were found with nOPV2 isolated in stool, 60-day residual paralysis; however, there were no definitive diagnostic

test performed to confirm VAPP (e.g., cerebrospinal fluid). In two cases the genetic sequence of nOPV2 found in stool was reported as having a low level of concern for mutation (in one case the results of genetic sequencing were not yet available).

- The datasets from Liberia, Benin, Congo, Tajikistan, Sierra Leone, and Niger were presented. In Liberia (1.8 million doses administered) there have been 42 AEFI detected to date and 12 were reviewed by the causality assessment committee, finding 9 ineligible cases and 0 consistent with causal association. One was classified as indeterminate. No AESIs were causally associated with the nOPV2 vaccine.. In Benin (4.5 million doses administered) there have been 2,931 AEFI detected to date and 137 were reviewed by the causality assessment committee, finding 9 indeterminate cases to follow up on and 0 consistent with causal association. Several cases that were previously categorized as consistent with causal association were recategorized to inconsistent with causal association to nOPV2. Note that no additional AEFIs were identified since the last GACVS report. In Congo (2.1 million doses administered) there have been 484 AEFI reported to date and 13 were reviewed by the causality assessment committee, finding 0 indeterminate cases to follow up on and 0 consistent with causal association. AESI surveillance was undertaken in all 40 reference hospitals across the country, but there is no information available at present. In Tajikistan (2.5 million doses administered) there have been 21 AEFI/AESI cases reported to date and 21 were reviewed by the causality assessment committee, finding 0 indeterminate cases to follow up on and 0 consistent with causal association. An independent consultant to the Ministry of Health prepared this summary of the causality assessment. In Sierra Leone (3.8 million doses administered) there have been 565 AEFIs reported to date and preliminary information indicated that 40 cases reported AFP. It was stated that 12 of these cases were reviewed by the NEC, who determined that 9 of the cases recovered. In one case, the child died due to an unspecified cause during a febrile illness. In two cases, the outcome was not stated. In Niger (8.7 million doses administered) the safety data is awaited.

- The nOPV2 genetic characterization group presented data from nOPV2 isolates from AFP cases, contacts, and environmental samples. **239** isolates have been confirmed to contain nOPV2: 89 from **Nigeria**, 77 isolates from **Tajikistan,** 17 from **Niger** 20 from **Sierra Leone**, 12 from **Liberia**, 11 from **Congo,** 11 from **Benin** and 2 from **Togo.** To date, the primary attenuation site (domain V) had **no changes** strengthening base pairing in any isolates and nOPV2 isolates contained between **0 and 5** VP1 nucleotide changes.
    - Each isolate is classified by the levels of concern on a scale from 1-9, with 9 representing the lowest level of concern. Of these isolates, 201 were classified as Category 8 and 32 isolates were classified as Category 9, indicating a low level of concern. The remaining 6 isolates were classified as Category 6, which is also considered a low level of concern.
    - The 6 nOPV2 isolates in category 6 were found to be recombinant between nOPV2 and Sabin 1 or NPEV. The recombination event might increase the chance for further recombination events, but it is not expected to have a substantial effect on virus attenuation.

- Laboratory studies indicate that none of the mutation combinations identified in nOPV2 isolates could cause the nOPV2 strain to approach the neurovirulence of Sabin 2.

GACVS sub-committee safety data assessment:

- The GACVS sub-committee appreciated the considerable efforts made to collect and present the safety data utilizing three separate data reporting systems.
- The committee noted a low rate of adverse events across the nOPV2 initial use countries and expressed reassurance from the data.
- Only in Nigeria has the NEC determined 6/583 AESI/AEFI cases to be consistent with a causal association: one case of anaphylaxis, one meningoencephalitis and one allergic reaction case, and three cases of suspected VAPP. The committee noted the cases were from 15 April to 2 August, 4 from Kebbi and 1 each from Rivers and Abia. There is no evidence to suggest any specific clustering spatial or temporal clustering of AESI reports. The 3 cases of suspected VAPP following ~44 million vaccinated children do not generate a new safety concern: the reporting rate of 0.007/100,000 vaccinees is below the expected range of 0.025-0.4 for Sabin OPV. The committee noted the other 3 AEFI/AESI cases (anaphylaxis, allergic reaction and meningo-encephalitis) have fully recovered and do not generate any new safety signals.
- The committee concluded that, based on the available date, 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 to be noted to the SAGE.
- The committee noted that AFP surveillance is functional and strong in most countries; however, the various countries differ in their capacity for surveillance.
- The Benin experience to monitor and detect AEFIs was highlighted as they were able to detect many AEFIs in the country.
- Finally, it was expressed that the committee's former recommendations were responded to in this presentation.
- The committee commented on the genetic sequencing data and the observation that recombinants had been detected (with none detected at the time of the last meeting) and asked if this increase in the rate of recombinants was concerning. It was noted that although there were 6 recombinant isolates, some were from the same sample, as there were 6 sequences from 3 samples. Furthermore, the recombinant affected two of the modifications of nOPV2: the hi-fi (sequence fidelity) and recombination mutations in the polymerase coding region. These modifications are not as critical as the other modifications (knock-out CRE region, the relocated CRE, and the domain V mutations). . It was also highlighted that recombination in polioviruses is very common. The committee noted that the genetic data confirmed what occurred in the clinical trials, which is reassuring.
- The committee expressed apprehension around missing data, noting that it is challenging to ascertain how much data is missing. It was also flagged that there may be questions or queries that are routinely missed. A concern was also expressed regarding incomplete cases. For example, in Sierra Leone, one child died due to an unspecified febrile disease and the outcome was not stated in two cases. The committee requested additional detail on these cases. Finally, there were cases reported with AFP-like symptoms that were judged to be non-associated

because of incomplete information. The committee raised that this is not the correct assessment.

Specific suggestions/notes from the committee moving forward:

- The committee reemphasized that AFP surveillance should remain the backbone of safety surveillance as it captures diseases that are most likely to be related to events of interest connected to nOPV2.
- It was noted that AESI surveillance is not contributing substantially to the reporting of adverse events and is expensive and time consuming.
    - The committee recommended that AESI surveillance be considered recommended but not required in countries that are resource constrained
    - The committee highlighted that AEFI and AFP surveillance should be strengthened in all countries before nOPV2 use; and non-AFP AESI surveillance conducted in countries that have the capacity and resources to do so.
    - The committee requested that an analysis be done to identify how many unique identified cases from AESI surveillance were not captured from AFP surveillance
- It was flagged that data harmonization should be a priority moving forward. Data collection should be cleaner, and standardizing surveillance could also be improved.
    - Electronic tools are an affordable and efficient solution for resource constrained countries. There could be applicable/relevant lessons to learn from the COVID-19 response.
    - The quality of surveillance should be analyzed and linked to the type/format of data collection tools.
    - It was suggested that a data mapping exercise could be useful to determine what tools are being used in which locations in order to have a more complete picture of the success of data collection.
- It was noted that a complete workup of all AFP cases is important and should be emphasized, including complete follow-up of cases and linkage with genetic sequencing of stool samples to determine whether mutations are occurring.
- The committee noted that the documentation from this meeting should be archived on the polio eradication website in order to share it with the global community.