GACVS (Global Advisory Committee on Vaccine Safety) Sub-Committee on nOPV2 Safety
August 3rd, 2021 – Virtual Meeting
Summary Note for the Record

Executive summary:

- The objectives of the meeting were: 1) to provide an update on the progress, status, and safety surveillance of the type 2 novel oral poliovirus vaccine (nOPV2) and 2) for the sub-committee to provide an independent assessment of nOPV2 safety data generated from initial use countries, which will inform SAGE's recommendation on the transition from initial use to wider use under EUL.

- Data was presented from four countries: Nigeria (39.2 million doses), Liberia (1.8 million doses), Benin (3.6 million doses) and Congo (1.9 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 July 2021, over which period 39.2 million doses were administered (a further 19.2 million doses were administered during July). In total, there were 225 AESIs reviewed by the national causality committee. There were 54/225 classified as ineligible, 2/225 unclassifiable and 160/255 as inconsistent with causal association, mostly due to conincidental illness or infection. There were 2/225 cases considered causally related – anaphylaxis and AFP (transverse myelitis or suspected vaccine-associated paralytic poliomyelitis (VAPP)) and 7/225 that were indeterminate pending follow-up for the next national causality meeting. [The rate of VAPP for Sabin OPV vaccines is estimated at 1 case per 4.1-4.6 million doses[1]].
    - The datasets from Liberia, Benin and Congo were presented but were less substantial. In Liberia (1.8 million doses administered) there have been 14 AESI detected to date and 12 were reviewed by the causality committee, finding 8 indeterminate cases to follow up on and 1 consistent causal association (pending follow-up). In Benin (3.6 million doses administered), there were 137 serious AEFIs assessed by the causality committee, which found 21 consistent causal association and 5 indeterminate cases. In Congo, there have been 202 AEFI reported, with 19 serious AEFIs; however, the causality assessment is yet to be conducted.

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[1] Kohler KA, Banerjee K, Gary Hlady W, Andrus JK, Sutter RW. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. Bull World Health Organ. 2002;80(3):210-6. PMID: 11984607; PMCID: PMC2567745.

- Data was presented from the nOPV2 genetic characterization group on nOPV2 isolates from AFP cases, contacts and environmental samples from Nigeria, Liberia and Benin. Out of 936 samples, 36 have been confirmed to contain nOPV2 with 66 pending NGS assessment. For the recent July report, 32 isolates were characterized (7 AFP, 15 AFP contacts and 10 environmental samples) from 3 countries (Nigeria, Liberia and Benin). For all 44 sequenced isolates (32 from July report, 12 from previous June report) the primary attenuation site (domain V) had no changes, and all isolates were non-recombinant. The few nOPV2 isolates that contained changes in the VP1 coding region (between 0 and 3 nucleotide mutations) were classified as low concern.
- In summary, the committee concluded that, based on the available data, there were no obvious red flags or safety concerns to date. The committee noted the substantial quantity of data available and vaccine doses successfully administered in the field; however, the documentation was inadequate and therefore the committee expressed apprehension especially regarding a large number of cases classified as indeterminate (7 in Nigeria, 8 in Liberia and 5 in Benin).

Safety data assessment:

- The GACVS sub-committee appreciated the considerable efforts made to collect and present the safety data and noted an improvement in the quality of data from the previous meeting. The sub-committee also noted the large amount of safety data available and the high number of nOPV2 doses, especially from Nigeria.
- Based on the data presented, the GACVS committee concluded that there were no safety "red flags" or clusters of AEFI that should be noted for concern to the SAGE WG.
- The committee noted there were only two causally associated cases which were identified in Nigeria (one anaphylaxis and one potential VAPP) and one case (history of fever, pending additional information) from Liberia. The diagnosis and classification of 20 cases (that included 2 deaths) that were identified from Benin need to be verified for the accuracy of case diagnosis and causality assessment methodology. Additionally, 19 serious AEFI cases were identified from Congo Brazzaville for which causality assessment is planned.
- In addition, data was presented from the nOPV2 genetic characterization group of nOPV2 isolates from stool samples and environmental surveillance. Out of 936 samples, 36 have been confirmed to contain nOPV2 with 66 pending NGS assessment. For the recent July report, 32 isolates were characterized (7 AFP, 15 AFP contacts and 10 environmental samples) from 3 countries (Nigeria, Liberia and Benin). For all 44 sequenced isolates (32 from July report, 12 from previous June report) the primary

attenuation site (domain V) had no changes, and all isolates were non-recombinant. The few nOPV2 isolates that contained changes in the VP1 coding region (between 0 and 3 nucleotide mutations) were classified as low concern.

- The committee expressed apprehension around the misclassification of cases particularly with consistent/ indeterminate cases/incomplete data as a caveat to the assessment. It was noted that there are several indeterminate cases (7 in Nigeria, 8 in Liberia and 5 in Benin) that are still requiring follow-up/additional information. For cases that have been determined as indeterminate, several have been diagnosed as transverse myelitis or GBS but lack sufficient clinical diagnostic data for the committee to evaluate the clinical diagnosis.

Specific suggestions/notes from the committee moving forward:

- The committee suggested that for moving forward into the wider use period, AFP surveillance should be the backbone of safety surveillance as it is well established and captures diseases that are most likely to be related to events of interest connected to nOPV2, such as vaccine-associated paralytic poliomyelitis, Guillain-Barré syndrome, transverse myelitis.
- The committee emphasised WHO should continue to strengthen the capacity at field level: both field workers and national causality committees.
    - It was noted that it is difficult for countries without robust health systems to conduct and document clinical tests such as electromyography to provide more specific clinical diagnoses.
    - It was suggested that moving forward a more standardized/simple guidance tool/ algorithm on processing identified AEFI/ AESI and AFP cases should be provided for national committees to have better clarity.
    - There is confusion in AESI classifications as per the WHO methodology, which should be corrected as soon as possible with additional trainings and capacity building.
    - The committee highlighted that the Benin data is an outlier: the committee requested there be a review and re-classification of AESIs and that the country is provided with support and training to review the data with an expert to improve the quality of AESI classification.
- In terms of data analysis, which was presented, it was requested that baseline figures (such as AFP reporting rate) would be more reliable if data was evaluated over several years, rather than choosing a specific year, such as 2020, especially because of the COVID impact on surveillance.
- In addition, it would be useful to provide summary statistics that can be compared across countries in a systematic manner (e.g., AESIs per 1 million doses administered). It

will also be important to standardize and clarify the denominators used in calculating the AFP rates.

- The committee cautioned that if roll-out of nOPV2 in the wider use period is too fast it could hamper the ability to identify signals/clusters/flags of concern.