GACVS (Global Advisory Committee of Vaccine Safety) Sub-Committee on nOPV2 Safety
June 30, 2022 – Virtual Meeting
Summary Note for the Record

The objective of this meeting was to provide an update of the progress, status, and safety surveillance of the type 2 novel oral poliovirus vaccine (nOPV2) under WHO Emergency Use Listing.

nOPV2 WG update

(S. Zipursky, WHO)

The nOPV working group presented an update on global nOPV2 usage. As of 30 June 2022, approximately 370 million doses of nOPV2 have been used across 21 countries. In addition to these 21 countries, there are 17 other countries that verified as ready to use nOPV2, 8 countries are in the verification progress, and discussions are ongoing with 7 other high-risk countries. An update on timing for clinical studies were provided, with results of the Phase III study in the Gambia expected in Q1 2023 and initial results of an immunogenicity study in naive infants in Bangladesh available in Q3 2022. In addition to clinical studies, serological surveys are being conducted to continue to assess nOPV2's effectiveness in protecting individuals from poliovirus; and epidemiological data is being analyzed to assess the vaccine's effectiveness in stopping outbreaks. The timeline was provided for nOPV2 licensure and WHO pre-qualification: with estimated submission during Q2 2023, with expected outcome of review Q4 2023/Q1 2024.

Uganda nOPV2 safety evaluation

Jane Gidudu (CDC)/ Fred Nsubuga (Uganda MoH)

There was an update on study: *Safety Evaluation of nOPV2 during a Supplemental Immunization Activity in Uganda.* The study objective is to identify and characterize safety events associated with nOPV2 vaccination using a multipronged approach of passive and active surveillance, including utilizing the routine, passive AEFI surveillance, time-limited active hospital-based surveillance for adverse events of special interest (AESI), and active cohort event monitoring (CEM). The study is close to completion with no major safety signals identified so far. The next steps are completion of data analysis, investigations (serious AEFI/AFPs) and causality assessment of pending serious AEFI/AFPs. The study results will be shared at the next GACVS-subcommittee meeting.

Genetic characterization data

Cara Burns (CDC)

The nOPV2 Genetic Characterization Group presented data from nOPV2 isolates from AFP cases, contacts, and environmental samples between June 2021 and April 2022. 325 isolates have been confirmed to contain nOPV2: 117 from Nigeria, 78 isolates from Tajikistan, 24 from Egypt, 21 from Sierra Leone, 18 from Uganda, 17 from Niger, 14 from Ethiopia, 12 from Liberia, 11 from Congo, 11 from Benin and 2 from Togo. 186/325 isolates are from acute flaccid paralysis (AFP) cases and contacts in relation to 146 distinct cases. Genetic sequencing of isolates has found to date: the primary attenuation site (domain V) had no changes strengthening base pairing in any isolates; most nOPV2 isolates were non-

recombinant but 8 recombinant isolates were identified; 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, 35 were classified as Category 9, 281 were classified as Category 8, 1 was classified as Category 7 and 8 classified as Category 6. The It was noted that Category 6 is considered a low level of concern.
- 8 nOPV2 isolates were found to be recombinant between nOPV2 and Sabin 1 or NPEV which imply loss of nOPV2 3D mutations. 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.

Field use safety data

Jo Lyn Chooi(P95)

A summary of cumulative safety data from 13 Mar 2021- 31 May 2022 was presented, alongside a detailed report developed for the GACVS sub-committee. This **observation period spans administration of approximately 253,000,000 doses of nOPV2 vaccine across 13 countries: Nigeria, Sierra Leone, Niger, Ethiopia, The Gambia, Mauritania, Senegal, Egypt, Uganda, Liberia, Benin, Congo, Tajikistan and Djibouti.** The current presentation provided safety data from new countries of Ethiopia, The Gambia, Mauritania, Senegal, Egypt and Uganda, as well as the pending safety data from the previous safety report from Nigeria, Sierra Leone, and Niger.

There have been **213 cases of the specified AESIs** reported across all countries and surveillance sources (note that these are **not all casually related**): 9 reports of anaphylaxis; 44 aseptic meningitis/encephalitis; 8 acute disseminated encephalomyelitis; 30 Guillain-Barré syndromes; 88 transverse myelitis; 5 AFP that are suspected vaccine-associated paralytic poliomyelitis (VAPP); 28 AFP that are vaccine-derived poliovirus type 2 (VDPV2); and 1 unexplained death. Based on administration of 253 million doses, the AESI reporting rate / 100,000 doses administered is lower than background incidence from published literature, and for VAPP lower than expected with the Sabin vaccine.

National Expert Committee classifications of serious cases with history of nOPV2 are detailed below (data on classifications are still awaited from 3 countries (Niger, Egypt and Ethiopia):

- **A1. Vaccine product-related reaction: 32**
- A2. Vaccine quality defect-related reaction: 0
- A3. Immunisation error-related reaction: 0
- A4. Immunisation anxiety-related reaction: 24
- B1. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event): 3
- B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunisation: 11
- C. Inconsistent with causal association to immunisation: 1005
- Ineligible: 180
- Unclassifiable: 35

- Downgraded to non-serious: 6
- Pending: 1

Of the 32 cases classified as A1, diagnoses are known for only 12 cases – 3 allergic reaction (Nigeria), 2 anaphylaxis (Nigeria), 5 suspected VAPP (5 Nigeria), 1 AFP (without further classification (Mauritania), 1 meningoencephalitis (Nigeria).

- Out of the 5 suspected VAPP cases, 2 are new reports (3 were previously reported in last GACVS meeting in February 2022): one case from Kebbi, Nigeria, with paralysis onset 30 days after 3rd nOPV2 dose, with nOPV2 isolated in stool and residual paralysis at 60 days; one case from Lagos Nigeria, paralysis onset 13 days after nOPV2 received, with nOPV2 isolated in stool and residual paralysis at 60 days. Both cases are awaiting genetic sequencing of stool isolates.
- It was noted that out of the 3 previous VAPP cases reported from Nigeria; 2 cases have recovered with no paralysis at follow up examinations 140-180 days from onset (although as they had residual paralysis at 60 days it meets VAPP criteria).
- The AFP case in Mauritania had paralysis onset on the day of nOPV2 administration; stool was positive for nOPV2, with 1 nucleotide difference in viral protein and no other poliovirus identified, and residual paralysis at 60 days.

Update on actions taken so far with respect to the subcommittee's recommendations from the previous nOPV2 GACVS subcommittee meeting and results of the mapping of data collection tools used by countries implementing nOPV2.

Comfort Ogar (WHO consultant)

The status of implementation of previous sub-committee recommendations was summarized, including updating guidance that active AESI surveillance is recommended but not mandatory for resource restrained countries, creating an online repository of GACVS sub-committee meeting reports, and conducing a mapping exercise to identify the tools used by countries to collect and analyze AEFI data, and to understand how GPEI partners can better support countries to improve the quality and timeliness of AEFI data particularly nOPV2 vaccine safety data.

A full report of the mapping exercise is available, and a summary provided here:

- The findings reveal that majority (78%) of countries that responded currently use a combination of paper-based and electronic tools for AEFI data collection. 64% of countries that use electronic reporting tools use 2 or more tools. Many countries tend to use multiple tools and, in some cases, different tools are used at the different administrative levels of data collection. Many of the responding countries (72%) expressed satisfaction with the electronic tools they have and 79% did not want to use an alternative tool. ODK Collect is the single most widely used tool by responding countries followed by VigiFlow.
- Because multiple electronic data collection tools are used at different levels within a country, improving interoperability of the different tools appears to be a necessary step for improving data timeliness and data quality.
- A few suggested next steps to harmonization of data collection tools are:
  1. Review nOPV2 AEFI training materials to ensure that the relevant tools used by many countries are included in the training curriculum

2. Organize refresher trainings for those involved in data collection, collation, and reporting and analysis making sure to include the key persons from the relevant organizations
3. Support countries to develop their own standard operating procedures (SOP) for data collection, collation and analysis.
4. Support countries to strengthen their support supervision and mentoring programs

GACVS sub-committee discussion and suggestions:

- The committee was pleased with the presentation of safety data from 13 countries with over 253 million nOPV2 doses and **concluded there were no safety red flags detected in the data that was presented.**
    - Given the volume of safety data, the committee members noted they may require more time to review the safety data report and share additional comments they may have after the meeting.
    - If the committee members have suggestions for alternative ways to present the increasing volume of safety data, they can contact the secretariat after the meeting. The secretariat will continue to ensure the safety data report is circulated at least one week in advance of the meeting for the committee to review.
        - Committee member suggested preparing the data as a manuscript would be useful.
- The committee expressed concern over the completeness of data for AEFI and AESI that seems to be an ongoing issue; specifically, that there was only a clinical diagnosis noted for 12/32 adverse events that were determined as A1. Vaccine product-related reaction: by National Expert Committees.
    - **The committee emphasized that efforts should be continued to get complete clinical and laboratory data so that the committee can make a reasonable assessment. The WG requested the nOPV2 WG to look into how the issue of missing clinical data in reported AESIs can be improved to provide more complete information which could assist in arriving at a correct diagnosis.**
- The committee noted that the AESI detection rate based on the number of administered doses are below background rates from the literature, and the total of 5 suspected VAPP cases (Nigeria) and 1 AFP case (Mauritania) are below the expected rate for Sabin OPV vaccine. The committee were pleased to note that 2/5 suspected VAPP cases that were reported at the last meeting have now recovered with no residual paralysis after subsequent follow-ups on 140-180 days after onset. The committee also noted that the 3/5 potential VAPP cases had no concerning genetic mutations/reversions (reported at the last meeting).
    - **The committee requested the pending information on genetic sequencing for the 2 newly reported cases be shared with them by email in follow up to this meeting.**
- The committee acknowledged the efforts from safety surveillance data to generate reporting rates of AESIs (using number of doses as the denominator as opposed to number of children, due to data limitations) and compare them to background expected rates.
    - **The committee requested that when the Uganda study is presented the number of cases is also calculated as a rate based on the relevant denominators.**

- The committee noted that the genetic characterization data was reassuring with no concerning mutations to date and continued monitored. There was an increase in the number of isolates with a recombination event: this was not observed early on; however, it was always expected to occur at some point. It was noted the combination events observed are relatively modest and less than 10-fold effect when assessed in-vitro.
- The committee were pleased to see the implementation of their previous recommendations.
    - It was noted that active AESI surveillance is now recommended but not mandatory for countries that are resourced constrained. The committee noted that the decision on whether to undertake AESI active surveillance is determined by the countries and the regional teams. If a country feels it has the capacity to do AESI surveillance, then it will include the requirements for that in the readiness verification process for nOPV2 deployment and the nOPV2 WG will assess the country accordingly.
- The committee congratulated the implementation of the mapping exercise and discussed that harmonizing data collection tools across different countries remains challenging.
    - A limitation of the survey was that around half of the responders were WHO staff or WHO consultants.
    - **The committee suggested the survey is directed more towards field-level staff doing the safety data collection, and the subsequent surveys also query the support available to field staff in case of a problem with electronic data applications**
    - **The committee noted that work should continue the efforts to achieve standardization of the tools that are used by countries.**
- The committee appreciated the update on other non-safety timelines, but noted they would also appreciate getting a broad overview of nOPV2 progress, beyond the safety aspect
    - **The committee requested that at the next meeting an update be provided on the broader context of nOPV2 development and field use beyond the safety aspect: updates on clinical studies, genetic analyses and field assessments of effectiveness (such as Tajikistan immunogenicity study, Liberia seroprevalence survey, case-control analysis and evidence of decreased circulation of cVDPV type 2).**