GACVS (Global Advisory Committee on Vaccine Safety) Sub-Committee on novel type 2 oral poliovirus vaccine (nOPV2) Safety
Assessment of nOPV2 Safety Data
24th January 2023 – Virtual Meeting
Summary Note for the Record

Summary of open meeting:

The GACVS Sub-Committee continues to provide an independent assessment of safety data generated from nOPV2 use throughout the duration of the nOPV2 EUL. The objective of this meeting is to provide an update on progress, status, and safety data on nOPV2.

Global nOPV2 update

The nOPV working group presented an update on global nOPV2 usage.

- Between March 2021 and January 2023, approximately 560m doses of nOPV2 have been administered across 26 countries (with 60% of doses administered in Nigeria). The full licensure of nOPV2 and WHO pre-qualification is targeted for the end of 2023.
- Most outbreaks have been stopped after 2 vaccination campaigns with nOPV2, with Nigeria a notable exception (approximately 70% of countries show no evidence of breakthrough transmission after 2 nOPV2 campaigns). There have been no circulating vaccine-derived poliovirus type 2 (cVDPV2) emergences linked to nOPV2 to-date, with a promising decline in the frequency of emergences since the 2019 peak.
- Safety and immunogenicity data were presented from the phase III clinical trial data in The Gambia, and the vaccine naive infant and concomitant use studies in Bangladesh. Neither study identified any safety concerns with nOPV2 use. Safety assessment has been conducted in observational studies during campaigns in The Gambia and Uganda (Uganda data is presented below, data from The Gambia will be presented at the next GACVS meeting).

Genetic Characterization Update

The nOPV2 genetic characterization sub-group presented data from 986 nOPV2 isolates nOPV2 isolates sequenced to date from 13 different countries from acute flaccid paralysis (AFP) cases, household contacts, primary immunodeficiency (PID) cases from environmental surveillance samples.

- Only one sample (3 isolates from same sample) have shown reversion at the primary attenuation sites (domain V and *cre*); due to recombination. By contrast, approximately 740 isolates (75%) would likely have shown such key domain V changes had the vaccine been Sabin OPV2.
- 47 nOPV2 isolates were found to be recombinant between nOPV2 and Sabin or species C enterovirus.
- 10 nOPV2 isolates were found to contain >5 VP1 nucleotide changes, but they were not genetically linked between them, and domain V was preserved.

There have been 49 nOPV2-positive isolates from four children with primary immunodeficiency from Egypt, none are AFP cases. Two patients found to excrete nOPV2 for long periods of time (191 and 309 days, respectively), which are classified as nOPV2 category #5 and iVDPV.

- The lack of change in nOPV2 primary attenuation site Domain V suggests that the relative risk of paralysis of these PID children would be lower than that from a fully reverted Sabin 2 virus
- Sustained replication of live attenuated vaccine viruses (including nOPV2) in a PID patient and resulting nucleotide changes are not unexpected findings but close follow up will be important to understand pattern of virus evolution over time and any other implications.

Uganda Observational Safety Study

The results of the safety study in Uganda were presented by the Centers for Disease Control (CDC) and the Uganda Ministry of Health.

- The objective of this study was to identify and characterize safety events associated with nOPV2 following mass vaccination in Uganda with both passive and active surveillance.
- The national passive surveillance system identified low numbers of both serious and non-serious adverse events following immunization (AEFI) and adverse events of special interest (AESI) with variability across regions.
- The available evidence points to no red flags following the nOPV2 national campaign.

Updated field use safety data

This current field safety data report provided a summary of new or updated data reported during the period between May 31, 2022, to October 31, 2022, from 13 countries (Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Cote d'Ivoire, Djibouti, Egypt, Ethiopia, Guinea Bissau, Mauritania, Mozambique, Niger, and Nigeria).

- From the first use of nOPV2 in March 2021 to the recent safety data lock of 31 October 2022, over 370 million doses of nOPV2 vaccine have been administered across 21 countries: Nigeria, Sierra Leone, Niger, Ethiopia, The Gambia, Mauritania, Senegal, Egypt, Uganda, Liberia, Benin, Republic of the Congo, Tajikistan, Djibouti, Mozambique, Cote D'Ivoire, Democratic Republic of the Congo, Guinea-Bissau, Chad, Cameroon and Central African Republic.
- AFP surveillance has been identified as being functional (at least 2 cases of non-polio AFP reported annually per 100,000 population aged less than 15 years) in 20 countries to date where safety data are available from nOPV2 immunisation campaigns conducted. It was below the minimum functionality only in Guinea Bissau with the rate of 1/100,000. AEFI surveillance varied in performance across the 21 countries where safety data are available. 18 of 21 countries reported conducting active AESI surveillance. Amongst the 18 countries that conducted active AESI surveillance, in 10 countries no confirmed AESIs were reported or there was no information on the findings of active surveillance.

- Based on the combined experience across countries for which safety data have so far been provided, there continues to be no evidence of any specific clusters or patterns of AEFI/AESI reports, either temporally or geographically, that would give rise to any unexpected safety concerns.
- The cumulative number of confirmed AESIs detected in countries where safety data are available remains low (268 total) in the context of over 370 million doses administered. Even conservatively assuming all AESIs to be causally related to nOPV2, estimated crude reporting rates from data available so far indicate rates lower than background incidence from published literature and therefore would not indicate an unexpected safety concern. For vaccine-associated paralytic poliomyelitis (VAPP), the reporting rate also indicates reporting rates lower than might be expected with the Sabin vaccine [0.005/100,000 doses for nOPV2 vs 0.025-0.4/100,000 for Sabin OPV).
- A total of 1529 adverse events with history of nOPV2 administration have been presented to National Causality Committees (or National Expert Committees) for review and classification. As of 31 October 2022, 60 cases have been classified as A1 (*vaccine product-related reaction)*; 27 cases classified as B1 (*temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event*); and one case as B2 (*qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization*). Of the 60 cases classified as A1 consistent with a causal association with nOPV2, the diagnosis or event terms are known for 58 cases. This includes 5 reports of suspected vaccine-associated paralytic poliomyelitis (AFP VAPP). Residual paralysis was present at the 60-day follow up for all 5 suspected VAPP cases, and genetic sequencing indicated a low level of concern for mutation per the classification scheme (categorized as Genetic Characterization Level). Three additional suspected VAPP cases were identified, categorized as AFP cases and not as VAPPs by the National Causality Committees of these countries, however they were assessed as causally related to nOPV2.

GACVS sub-committee conclusions and recommendations:

- The GACVS sub-committee appreciated the considerable efforts made to collect and present the safety data.
- 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 several incorrect classifications of cases that require review by National Causality Committees or additional clarification, including:
    - Several cases that provided only symptoms instead of a diagnosis. The committee noted many cases diagnosed as acute flaccid paralysis (AFP); however, AFP is a syndrome, not a diagnosis.
    - An A1 AFP case with paralysis onset the same day as vaccination (timing would indicate this is co-incidental) to be reviewed.

    - Several AFP and neurological cases presented from Ethiopia, where the committee requested that a review is conducted on how much clinical data was available at time of assessment.
    - An unexplained death that incorrectly classified as A1, when cause of death was not known.
    - Several GBS, AFP and ADEM cases classified as B; however, these are specified AESIs of the vaccine so not appropriate for B1 classification.
    - Several gastroenteritis cases classified as A1; however, information on further testing necessary to arrive at this classification was not provided.
- The committee requested that as a priority follow up is done on cases from causality assessment with missing clinical information.
- The committee emphasized that high quality monitoring and analysis must continue in both areas of safety and genetic stability, as specifically for the later, the risk of detecting concerning variants will increase over time.
    - The committee recommended that work continues to support strengthening AFP and AEFI surveillance as well as the capacity of national causality committees to improve completeness of reporting, correctness of classifications and timeliness.
    - The committee recommended that an analysis of the temporal information for both safety and genetic stability be carried out.
        - It was suggested to stratify safety and genetic stability data by time-since-immunization to give a sense of the patterns over time.
        - Specifically with the genetic stability data, the committee felt it would be useful to put in the context what evolution we see over time since campaigns, and what we would expect to see with mOPV2 by comparison.
- The committee were concerned over the continuing cVDPV2 outbreaks in Nigeria despite multiple nOPV2 campaigns; however, they noted the primary reason is likely poor coverage and that other advisory boards are providing advice and analysis on the situation. Additionally, they were re-assured that none of the cVDPV2 emergences seen in Nigeria to-date are derived from nOPV2.
- The committee noted background rates from literature are used here and are not specific for location or age group, which should be noted when comparisons are made. The committee noted that it would be very useful to have specific background rates from the countries using nOPV2, and any work towards this would be useful. It was noted that an effort is underway to try to provide more specific background rates of adverse events in the broader context of vaccine safety monitoring.