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 - July 18, 2024

The final meeting of the GACVS sub-committee on nOPV2 safety was conducted virtually on July 18, 2024, to review the progress of nOPV2 roll-out and evaluate the safety profile of the vaccine using updated safety data from all campaigns conducted during the Emergency Use Listing (EUL) authorization period between March 2021 and December 2023. The notes for record presented below summarize the key presentations, discussions and conclusions from the meeting.

Update on the roll-out of nOPV2 under EUL:

- nOPV2 has traversed a long journey, starting from initial grants to convene a global consortium for its development in 2011. It became the first vaccine to transition from WHO EUL to WHO prequalification (PQ) use based on extensive clinical and field data monitoring in December 2024.
- By July 18, 2024, 1.2 billion doses of nOPV2 have been administered in 41 countries. During 2023, nOPV2 was the vaccine of choice in 98% campaigns conducted in response to circulating vaccine derived poliovirus type-2 (cVDPV2) outbreaks.
- Demand for nOPV2 exceeded supply from the current manufacturer, Bio Farma, at times during the first half of 2024. To mitigate this risk, a second supplier, Biological E has submitted a dossier for WHO prequalification in January 2024, with support from the Global Polio Eradication Initiative (GPEI). The manufacturer is expected to contribute to additional supply of nOPV2 by the third quarter of 2024.
- Following nOPV2 PQ in 2023, vaccine performance monitoring, including surveillance and whole genome sequencing has been conducted consistent with processes followed for other oral polio vaccines (OPVs). As enhanced safety monitoring is no longer mandatory, countries using nOPV2 are no longer mandated to submit safety monitoring data to GPEI, however, countries should continue to monitor safety of the vaccine as per routine procedures in place for all other vaccines.
- nOPV2 field data continues to indicate a favorable safety, immunogenicity and enhanced genetic stability profile.

Genetic Characterization Update:

The genetic characterization update was presented in three parts: first, an update on the genetic analysis of available nOPV2 isolates during the EUL period; second, a report on nOPV2-derived emergences; and finally, the latest findings from an Imperial College modeling study analyzing risk factors for emergences.

- As of December 31, 2023, the whole genome sequence of 2,281 nOPV2 isolates from 29 different countries were analyzed. Most isolates analyzed through whole genome sequencing indicate no or minimal changes in the genetic structure of nOPV2.
- 110 (5%) of all whole genome sequenced isolates were category 1 or 2, i.e., showing key genetic modifications of nOPV2 including Domain V, due to recombination events. 89 of these isolates are linked to 11 cVDPV2 groups, indicative of a spread of previous reversion event, rather than a new reversion event.
- Domain V was lost in 1.5% of isolates linked to nOPV2, as opposed to an expected 75% of monovalent OPV2.
- Two patients with preliminary immunodeficiency disorder (PID) were found to excrete nOPV2 for long periods of time. While one patient ceased excreting after 338 days, the other continues to excrete nOPV2 after 595 days.
- As of 27 June 2024, a total of 17 nOPV2 linked cVDPV2 emergence groups have been detected, in DRC (with detections in Burundi, Zambia, Tanzania, Cote d'Ivoire, Angola, and Congo, and Mozambique), the Central African Republic, Nigeria, Egypt, Botswana, Cameroon (with a detection in Chad), Zimbabwe, South Sudan, Angola, and Ethiopia. These emergence groups have been collectively linked to 113 cases of AFP to date. Most of the recorded AFP cases (66%) came from two emergence groups in the DRC, while all other emergences had 0 to 7 linked AFP cases. Of these 17 emergences of cVDPV2 derived from nOPV2, one was detected in 2021, two were detected in 2022, 12 were detected in 2023, and two have been detected in 2024.
- The observed number of emergences were compared to estimated risk of emergences based on an analytical framework[1] that considers several factors, including, campaign size, pre-campaign immunity, and expected time to discovery of emergences based on campaign data, and presence of environmental surveillance, along with other relevant factors.

[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

- Based on this framework, if nOPV2 seeded new emergences at the same rate as Sabin OPV2, 131 cVDPV2 emergences related to nOPV2 would be seeded, given total nOPV2 use to date in the African region. Considering time-to-discovery, approximately 70 of the index isolates for nOPV2-derived cVDPV2 emergences would be expected to be seen by 11 April 2024
- The 13 observed nOPV2 derived cVDPV2 emergences African region are an estimated 81% (75%-85%) lower than expected if seeding at Sabin OPV2 rate.
- A hierarchical spatiotemporal model was presented to evaluate the influence of risk factors such as campaign size, existing type-2 immunity, maximum travel time to nearest health facility, seasonality, vaccine type (Sabin versus novel OPV2), and type of campaign (singleton versus multiple) on the risk of emergences (expansion of previous work[2]).
- Results from this analysis suggest nOPV2 campaigns are associated on average with 77% (56%-90%) reduction in risk of emergences, compared with similar Sabin OPV2 campaigns. This risk may be further reduced by considering modifiable risk factors, such as avoiding singleton campaigns in areas of low immunity.
- In conclusion, findings from field monitoring of genetic stability of nOPV2 coupled with two analyses comparing the risk of emergences between nOPV2 and Sabin OPV2 indicate that nOPV2 continues to demonstrate enhanced genetic stability and significantly lower likelihood of reversion to neurovirulence compared to Sabin OPV2.

Cumulative field use safety data under EUL:

A summary of the 6th nOPV2 safety report which covered campaigns conducted during the EUL period from 13th March 2021 to 26th December 2024 was presented.

- The report included data from 165 campaigns, and 1,018,755,412 doses of nOPV2 administered, across 35 countries in Africa and Asia.
- Data quality and completeness:
    - AFP surveillance was done in all countries, with 31 countries displaying functional AFP surveillance (*i.e.*, more than 2 non-polio AFP cases per 100,000 children < 15 years per year).
    - While all countries implemented passive AEFI surveillance, 27 of 35 countries reported adverse events from this surveillance system. 21 out of 35 countries reported at least 1

[2] Gray EJ, Cooper LV, Bandyopadhyay AS, Blake IM, Grassly NC. The Origins and Risk Factors for Serotype-2 Vaccine-Derived Poliovirus Emergences in Africa During 2016-2019. *J Infect Dis*. 2023;228(1):80-88. doi:10.1093/infdis/jiad004

serious AEFI case per million total population to VigiBase, indicating a functional AEFI surveillance system[3], as per global benchmarks.

- Active AESI surveillance was implemented in 19 out of 35 countries, although 5 countries discontinued AESI surveillance after having implemented it for earlier vaccination campaigns. Most countries reported less than 1 case per 100,000 vaccinations, with 5 countries not finding any potential AESIs or being unable to report data from that surveillance system.
- In total, 12,499 cases were reported through all surveillance systems, with 3,064 (25%) of them as serious, while seriousness was not known for 2% (n=293) cases. These 3,064 serious cases contain a total of 4,847 events, with each case containing 1.6 events on average. The date of vaccination was not reported for 778 (6%) of total cases, while 783 (26%) serious cases did not have a reported final diagnosis or valid diagnosis.
- Out of 35 countries, 25 have presented cases for national expert committee (NEC) evaluation. Of the remainder, 5 countries did not report any serious events, while 5 countries reported serious events, but no NEC assessments were shared. Out of 3,064 serious cases, 70% were presented to the NEC and assessment results have been shared.
- Among all campaigns, data was received for 98% AFP, 94% AEFI, 91% AESI and 78% NEC line lists. This is a drastic improvement over the previous, 5th, report, where data were received for 75% AFP, 72% AEFI, 71% AESI and 58% NEC line lists.

- In total 19,158 AEFIs (including serious and non-serious events) were reported throughout the entire EUL safety surveillance period of nOPV2. There were 17% more events reported in males compared to females, and the median age was 2.2 years. The AEFI reporting rate varied between 89-0.01 AEFIs per 100,000 nOPV2 doses.
- The ten most common AEFIs were, by latest diagnosis (with reporting rates per 100,000 administered doses): Pyrexia (0.75), diarrhoea (0.16), vomiting (0.15), cough (0.14), malaria (0.05), rhinorrhoea (0.04) abdominal pain (0.03), fatigue (0.03), neuritis (0.03) and Adverse Event NOS (not otherwise specified) (0.03).
- To date, 4,847 events (including AESIs) have been recorded as serious by their latest assessment. The most frequently reported SAE was pyrexia, a common reaction to vaccination, accounting for 12% (n=566) of the cases. Malaria was the second most common, comprising 10% (n=481) of the reported SAES. Other significant SAEs included neuritis (5%, n=256), seizures (3%, n=157), monoparesis (3%, n=143), and acute flaccid paralysis (3%, n=121).

[3] WHO Weekly Epidemiological Record of 11 August 2023

- NEC assessments have been reported for 2,145 events for all countries, of which 2,039 received a graded assessment from grade A1 (vaccine product related reaction) to grade C (coincidental). Of these 2,039 events, 1837 (90%) were assessed as coincidental to nOPV2 vaccination. The remaining 99 (4%) events were deemed unclassifiable, invalid for assessment or downgraded to non-serious.
- To date, 157 cases have been classified as either vaccine product-related (A1, n=108 cases) or temporally related (B1, n=49 cases) to nOPV2. Cases of Guillain–Barré syndrome (GBS, n=19) and Acute Flaccid Paralysis (AFP, n=16) were most frequently classified diagnoses as A1 or B1.
- There have been 5 confirmed VAPP cases, all from Nigeria. Additionally, there are 4 discarded cases of suspected VAPP from Cameroon. These cases have 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)[4] and 0.02/100,000 for bivalent oral polio vaccine (bOPV)[5].
- Overall, there have been 697 AESIs reported by all countries. For several AESIs a significant or majority share was reported for certain countries, as observed for anaphylaxis (35% in Cameroon), encephalitis (62% in Egypt and CAR), meningitis (47% in Egypt), GBS (46% in Somalia and Tanzania), as well as myelitis (93% in Nigeria, Somalia and Tanzania). These observed clusters might be influenced by local health practices, and no significant pattern or signal was identified. Overall, the global AEFI rates were within or below the background rates for these events in background literature.
- With data from 35 countries and over a billion doses, there continues to be no evidence of any clusters or patterns of adverse event reports, either temporally or geographically, that would give rise to any unexpected safety concerns.
- **Temporal analysis findings:**
    - A temporal analysis was undertaken to delineate time to onset of all AEFIs with a valid or final diagnosis reported post nOPV2 vaccination between March 2021-Dec 2023, under the direction of the sub-committee
    - From all serious AEFIs with a valid or final diagnosis, an analytical subset was developed excluding those with:
        - Less than 10 events reported

[4] cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/polio-vaccine-rates-information-sheet.pdf
[5] Gao et al, Br J Clin Pharmacol. 2021 Dec;87(12):4831-4838. pubmed.ncbi.nlm.nih.gov/34240463/

- Events such as cVDPV2 where identification of index child is not feasible in the safety database; and infections, except measles and malaria which were included as control conditions
- Events with implausible or missing vaccination or event onset dates

- Primary and secondary risk windows were identified based on literature review and feedback from the sub-committee.
- The median time to onset and inter-quartile range (IQR) were calculated for the final sample of all events, as well as events within primary and secondary risk windows. The results from this analysis are described in table 1 below:

Table 1: Median time to onset (IQR) of selected serious adverse events following nOPV2 vaccination reported between March 2021-December 2023

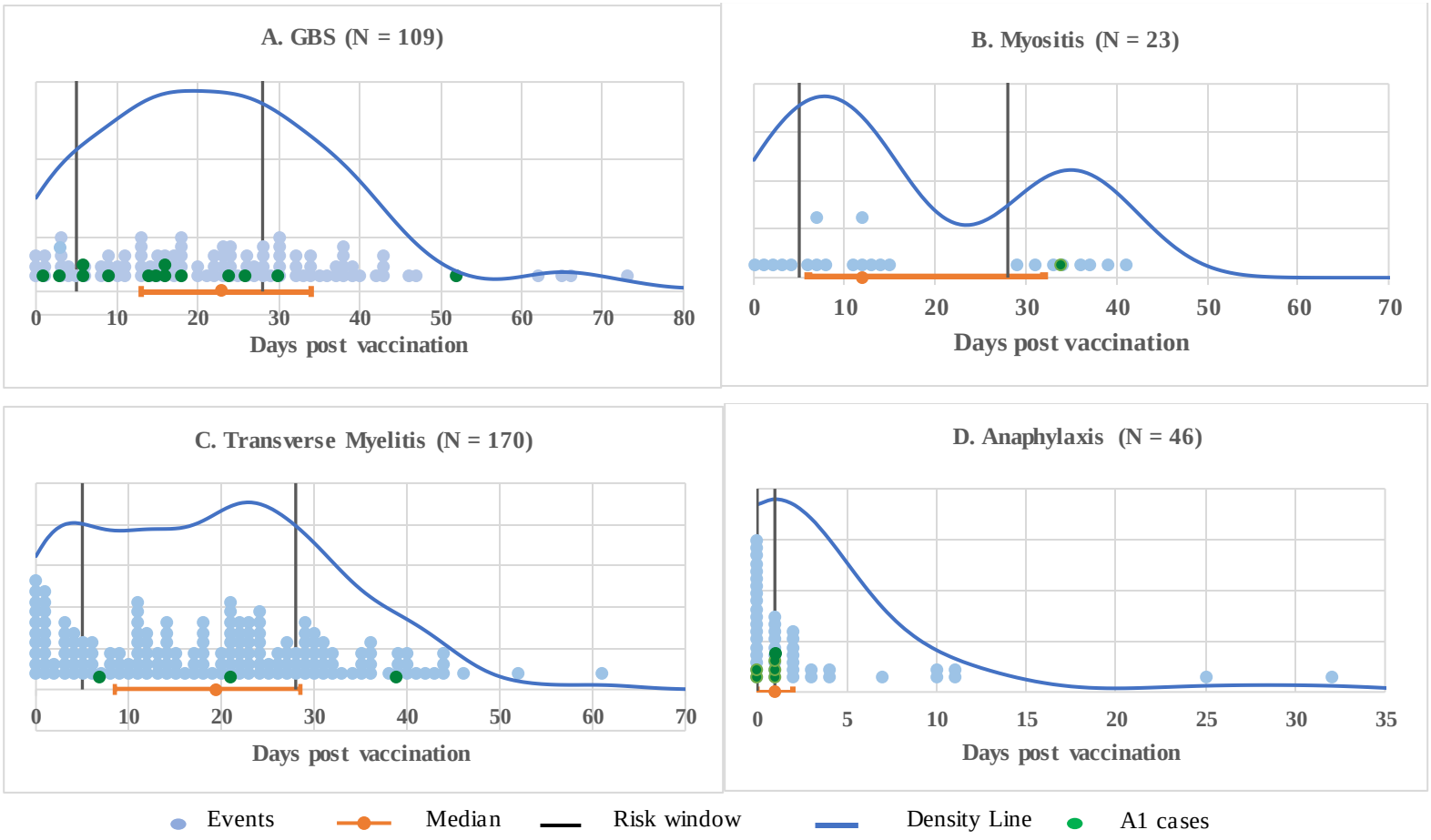
	Total (all positive dates)			Primary analysis			Secondary analysis		
MedDRA Preferred Term	**Total Events**	**Events (n)**	**Median Days (IQR)**	**Risk Window**	**Events (n)**	**Median Days (IQR)**	**Risk Window**	**Events (n)**	**Median Days (IQR)**
Neuritis	**275**	251	21 (9-31)	2 - 42	**226**	21 (10-29.7)	5 - 28	**145**	16 (9-24)
Seizure	**203**	184	3 (0-11)	0 - 10	**127**	0 (0-3)	7 - 10	**8**	8 (7-9.2)
Meningoencephalitis	**161**	153	12 (1-24)	2 - 42	**110**	18 (9-27.7)	5 - 28	**72**	15 (9-20)
Myelitis (transverse)	**189**	170	19.5 (8-28.75)	2 - 42	**144**	21 (11-28.2)	5 - 28	**95**	18 (11-23)
Febrile convulsion	**117**	109	10 (1-28)	0 - 10	**55**	1 (0-2.5)	7 - 10	**5**	8 (7-9)
Guillain-Barre syndrome	**117**	109	23 (13-34)	2 - 42	**90**	22 (13-30)	5 - 28	**58**	17.5 (13-23)
Meningitis (aseptic)	**109**	106	13 (3.2-28.7)	2 - 42	**88**	14 (6-29.2)	5 - 28	**48**	13 (8-19.2)
Anaphylactic reaction	**48**	46	1 (0-2)	0 - 2	**35**	0 (0-1)	0 - 1	**28**	0 (0-1)
Myositis	**25**	23	12 (6.5-32)	0 - 42	**23**	12 (6.5-32)	5 - 28	**10**	11.5 (7.2-12.7)
Acute Demyelinating Encephalomyelitis	**10**	10	26 (3-44.2)	2 - 42	**7**	6 (1-26)	5 - 28	**2**	13.5 (9.7-17.2)
Malaria – Control*	**521**	501	14 (3-9)	0 – 45*	**470**	11 (2-28)	0 - 45	**470**	11 (2-28)
Measles – Control*	**39**	36	15 (7.7-26.5)	0 - 45	**34**	13 (7-25)	0 - 45	**33**	13 (7-25)

*Control conditions do not have risk windows *per se*, upper limit is 45 days for the 6-week surveillance period + 3 days of vaccination

- For every preferred term, each single event was plotted in a graph by day of onset and a cumulative curve was applied as visual representation of distribution of events by days post vaccination.
- As observed in the findings in Figure 1 below, more events are reported immediately after vaccination, regardless of whether it is a case or control condition, and many A1 cases tended to occur outside the risk-window. Many events, display a secondary peak, 20-25 days post vaccination. Conditions such as transverse myelitis, GBS and neuritis are most evenly distributed.

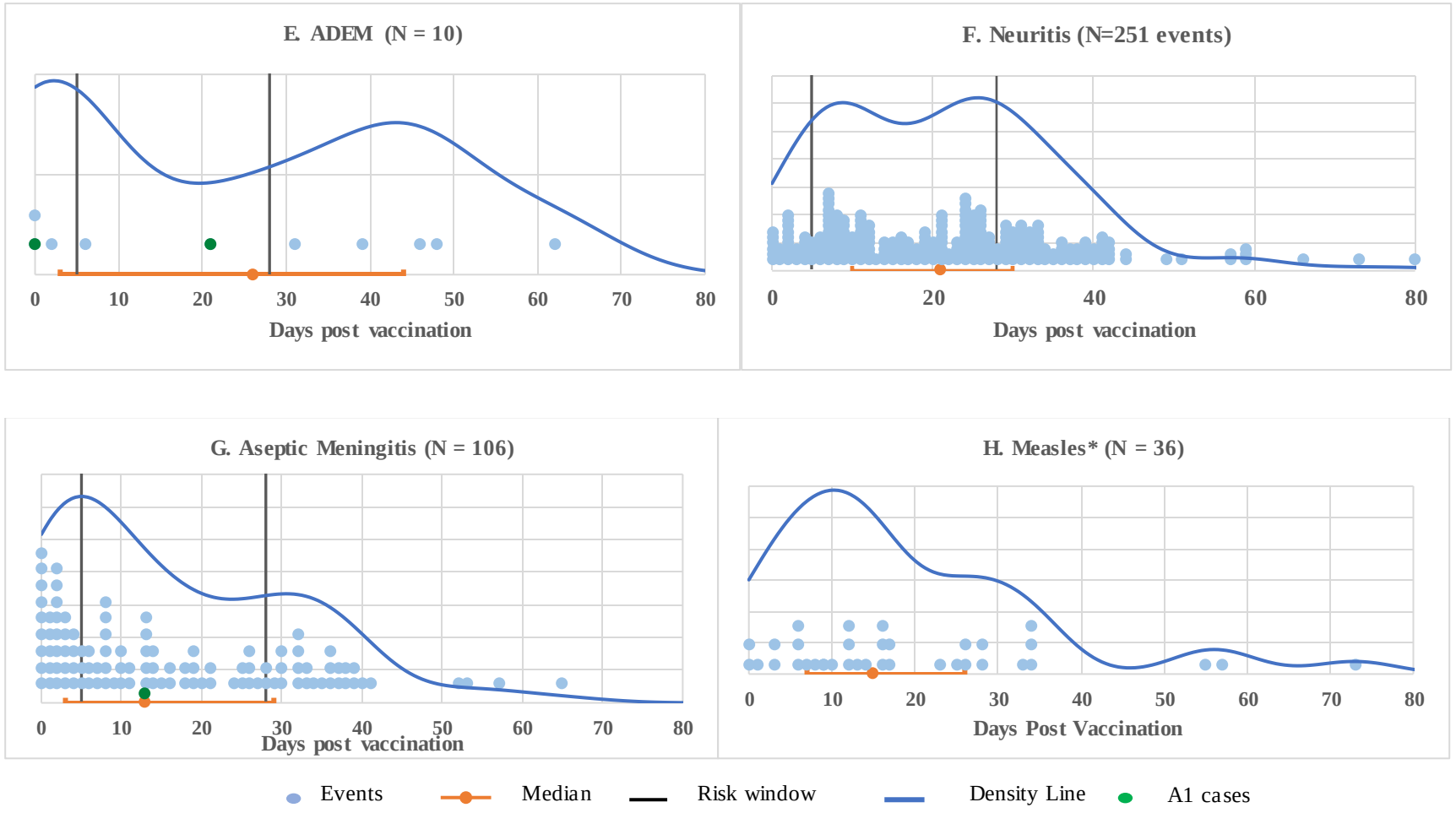
- Limited data quality and completion preclude the assessment of levels of diagnostic certainty for the selected events.
- The temporal analysis did not highlight any significant safety signals among the AEFIs reported post nOPV2 under the EUL.

Figure 1: Distribution of individual adverse events by number of days post nOPV2 vaccination, density line and median days post vaccination for: A- Guillain–Barré syndrome; B-Myositis; C-Transverse Myelitis; D-Anaphylaxis; E-Acute Demyelinating Encephalomyelitis; F-Neuritis; G-Aseptic Meningitis, H-Measles; I-Seizure; J-Febrile Convulsion; K-Malaria; and L- Encephalitis



Abbreviations: GBS- Guillain–Barré syndrome

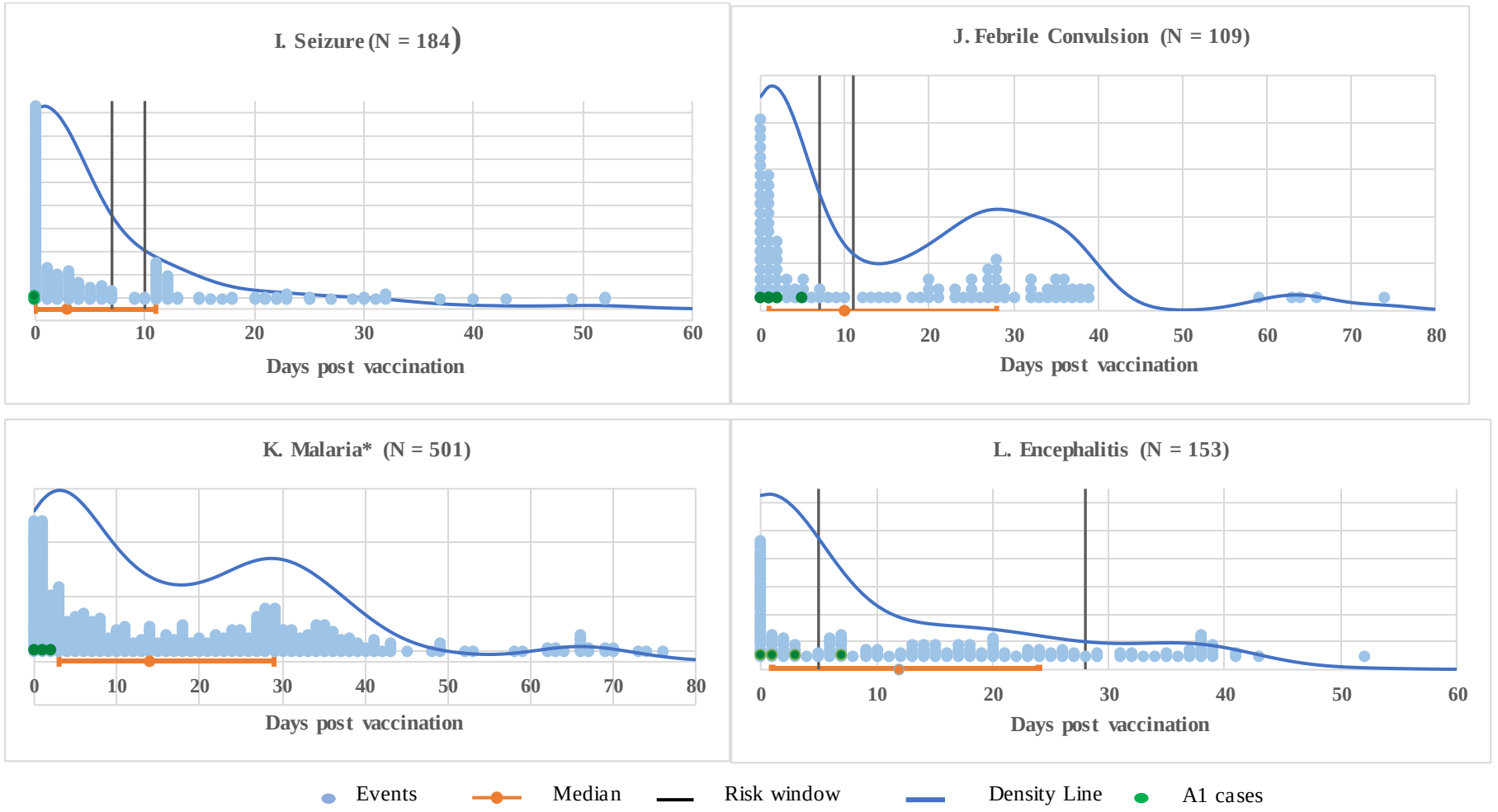
Figure 2: Distribution of individual adverse events by number of days post nOPV2 vaccination, density line and median days post vaccination for: A- Guillain–Barré syndrome; B-Myositis; C-Transverse Myelitis; D-Anaphylaxis; E-Acute Demyelinating Encephalomyelitis; F-Neuritis; G-Aseptic Meningitis, H-Measles; I-Seizure; J-Febrile Convulsion; K-Malaria; and L- Encephalitis



* Control Condition

Abbreviations: ADEM- Acute Demyelinating Encephalomyelitis

Figure 3: Distribution of individual adverse events by number of days post nOPV2 vaccination, density line and median days post vaccination for: A- Guillain–Barré syndrome; B-Myositis; C-Transverse Myelitis; D-Anaphylaxis; E-Acute Demyelinating Encephalomyelitis; F-Neuritis; G-Aseptic Meningitis, H-Measles; I-Seizure; J-Febrile Convulsion; K-Malaria; and L- Encephalitis



* Control Condition

- **Follow-up on Benin Safety Incident:**
    - A safety investigation was triggered due to reports of large number of AEFIs reporting during an nOPV2 campaign in Benin in October 2022, particularly 2 early cases of Quincke's oedema in preterm infants.
    - An update regarding this issue was last presented by WHO regional office pharmacovigilance team in the GACVS's meeting on 15-16 May 2023. The update clarified that the country's NEC assessed only 3 cases to be A1 (including both cases of Quincke's oedema). Moreover, samples of identified batches were found to have no contamination or findings of concern[6].
    - Despite multiple attempts to follow-up, no further reports have been made available by the country regarding this incident. The sub-committee's feedback and guidance was sought for formal resolution of this event (refer point 9 in discussion and key recommendation section for feedback from the sub-committee).

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

The following actions were undertaken to address previous recommendations[7] from the sub-committee:

- **Prioritize completion of pending causality assessments, particularly neurological events:** The global and regional pharmacovigilance team and nOPV2 safety focal points collaborated to facilitate the completion of pending causality assessments. Country and case-wise data trackers were prepared and pending safety data requests were escalated to regional and country counterparts. Data reconciliation exercises were conducted, which helped eliminate duplications, and data errors. The nOPV2 regional safety focal point also visited Nigeria in-person and supported investigation and classification of remaining serious AEFIs in Brazzaville. Due to these efforts, causality assessment line lists were received for 78% of all campaigns conducted during the EUL period, a significant improvement from 47% completion in the previous report.
- **Geographic and demographic distribution of AEFIs, AESIs, and causality assessments** were presented in the 6th nOPV2 safety report as directed by the sub-committee. An updated temporal analysis (described above) was also presented.
- **Comparative analysis of Vigibase and GPEI database on nOPV2 safety**: In its previous meeting, the sub-committee had discussed the need to address concerns about data availability

[6] **Report of the Meeting of the WHO Global Advisory Committee on Vaccine Safety, 15–16 May 2023.** Weekly Epidemiological Record, World Health Organization, WER N°32, 2023, 98, 345–354

[7] **Notes-for-record-5th-GACVS-nOPV2-20240318.pdf (polioeradication.org)**

during rollout of nOPV2 following pre-qualification to new countries. As countries are no longer mandated to submit nOPV2 safety data to GPEI, the sub-committee members expressed concern regarding the sudden withdrawal of global oversight on nOPV2 safety after prequalification. The sub-committee had suggested periodic monitoring of Vigibase data for reports of nOPV2 related AEFIs and requested the secretariat for a comparative analysis of the Vigibase and GPEI safety databases to assess its quality, completeness and suitability for sustained monitoring. The comparative analysis revealed that nOPV2 related AEFI reports could be identified from the Vigibase database in 32 out of 35 countries which conducted campaigns during the EUL period. While Vigibase contained 21% more cumulative AEFIs compared to the GPEI safety surveillance database, it lacked granular causality assessment data, and contained no or fewer reports of AEFIs primarily identified through AFP surveillance system, including Vaccine associated paralytic polio (VAPP), and acute demyelinating encephalomyelitis (ADEM).

Discussion and key recommendations:

1. The sub-committee noted that out of the approximately 2300 nOPV2 isolates, 89 showed a domain V replacement, and requested clarification regarding the efforts required for interrupt transmission of these mutated variants. It was clarified that once the vaccine virus evolves into a strain that has lost domain V, the outbreak trends do not differ significantly from those caused by Sabin OPV strains. However, there is a substantial reduction in the initiation of outbreaks compared to Sabin OPV strains. The focus is on monitoring the risk of international spread, the paralytic burden of these outbreaks, and the number of campaigns needed to stop them.
2. The sub-committee requested more information regarding the origins of the recombination among emergences with domain V mutations, and whether they were related to circulating type 1 and 3 polioviruses. Experts clarified that the recombination has occurred with non-polio enteroviruses which have not been fully identified, as genomic sequences of current species C enteroviruses are lacking. The nOPV2-derived cVDPV emergences generally align with this subset of Coxsackie A viruses, indicating a pattern of recombination within species C.
3. Members of the sub-committee also requested for clarification regarding the benefits of nOPV2 versus inactivated polio vaccine (IPV) to contain cVDPV2 outbreaks in the future, particularly for nations that have not used OPV2 for a long-time following the switch in 2016. Experts noted that both options carry some risks: while IPV does not carry the risk of cVDPVs, it does not confer adequate gut immunity which is vital for interrupting transmission, and at the same time, while the risk of cVDPV2 emergence is much lower in nOPV2 compared to Sabin OPV2, it is not nil. The experts clarified that the appropriate vaccine choice would be informed by factors including the

force of the infection, transmission dynamics such as the number of environmental isolates and cases of acute flaccid paralysis (AFP) identified, as well as existing mucosal and humoral immunity levels in the population. Experts also clarified that IPV and nOPV2 may be used together or in quick succession during an outbreak in settings where outbreaks persist beyond a standard OPV response.

4. The sub-committee inquired about the prescribed containment measures following an nOPV2 campaign. Experts clarified that the containment strategies for nOPV2 are similar to those for other live OPVs. Although nOPV2 is currently under a temporary waiver from the containment advisory group, standard recommendations still apply, such as managing and accounting for vaccine vials. The vaccine's genetic stability is a factor in this temporary waiver.
5. Regarding factors influencing campaign size, experts clarified that the response to cVDPV2 outbreaks is consistent regardless of the virus's origin. A typical response involves a two-round supplementary immunization activity, but this can extend to three rounds based on the outbreak's scope. The size of the campaign depends on the outbreak's location (urban or rural). Detection of a cVDPV2 strain often triggers a national response, with campaign scope adjusting according to the supply situation and outbreak severity.
6. The sub-committee was interested to gain insights regarding the perceived low rate of emergences in Nigeria, which consumed nearly 50% of the global nOPV2 supply, and requested for more information regarding the available data on the effectiveness of nOPV2 in interrupting cVDPV2 outbreaks in the country. The experts clarified that key factors contributing to low nOPV2 emergence risk in Nigeria include multiple campaign rounds, campaign size, higher campaign quality, potentially low prevalence of non-polio enteroviruses compared to other countries (such as Democratic Republic of Congo and Central African Republic), as well as lower travel time to health facilities which influence the risk of seeding new emergences. The experts also clarified that previous case-control[8] and time-series model studies[9] have demonstrated that effectiveness of nOPV2 is like the Sabin OPV2 in controlling cVDPV2 outbreaks.
7. The sub-committee members expressed concern regarding the long-term supply of nOPV2, highlighting reluctance in some countries to use mOPV2 in response to cVDPV2 outbreaks. Experts clarified that efforts are in place to maintain and secure nOPV2 supplies through a

[8] Cooper LV, Erbeto TB, Danzomo AA, Abdullahi HW, Boateng K, Adamu US, Shuaib F, Modjirom N, Gray EJ, Bandyopadhyay AS, Zipursky S, Okiror SO, Grassly NC, Blake IM. Effectiveness of poliovirus vaccines against circulating vaccine-derived type 2 poliomyelitis in Nigeria between 2017 and 2022: a case-control study. Lancet Infect Dis. 2024 Apr;24(4):427-436. doi: 10.1016/S1473-3099(23)00688-6. Epub 2024 Jan 18. PMID: 38246190.

[9] Arend Voorman, Hil Lyons, Faisal Shuaib, Usman S Adamu, Charles Korir, Tesfaye Erbeto, Ananda S Bandyopadhyay, Samuel Okiror, Impact of Supplementary Immunization Activities using Novel Oral Polio Vaccine Type 2 during a Large outbreak of Circulating Vaccine-Derived Poliovirus in Nigeria, *The Journal of Infectious Diseases*, Volume 229, Issue 3, 15 March 2024, Pages 805–812, https://doi.org/10.1093/infdis/jiad222

partnership with Bio Farma and the addition of a second supplier, Biological E. The plan includes sustaining the nOPV2 stockpile even after the outbreak is under control. In the event of a supply shortage, it is crucial to respond with available vaccines, whether nOPV2 or mOPV2.

8. The sub-committee members appreciated the insights from the temporal analysis, as well as the risk-window approach undertaken for identification of potential safety signals. The similar distribution of the occurrence of AEFI and control conditions highlighted potential confounding factors, including bias towards increased reporting of all perceived adverse events regardless of correlation to vaccination, immediately post vaccination, and underreporting of events with long-term sequelae. Further, they noted that several reported events occurred outside the risk windows prescribed by background literature. The experts added that the findings from the temporal analysis have limited generalizability due to inability to assess levels of diagnostic certainty and reported cases, challenges in quality and completeness of collected data, and limited sample size for select adverse events such as GBS and measles. Nevertheless, the findings will enrich the currently limited evidence base on risk-windows for reported AEFIs from low- and middle-income country (LMIC) settings and will be useful for future vaccine safety evaluations.
9. Regarding the safety incident from Benin the committee noted that despite ongoing difficulty in obtaining nOPV2 safety information from the country, it recently conducted a campaign with the vaccine in the first week of June. Multiple attempts have been made to get the necessary information, including personal meetings with key figures. Despite these efforts, no additional information has been provided. Acknowledging the country's constraints, and the lack of response, the sub-committee agreed to close the ongoing investigation.
10. Regarding the recommendation to continue periodic review of Vigibase nOPV2 safety data, the sub-committee concluded that:
    a. Despite observed variations, Vigibase is a useful and suitable source for continued monitoring of nOPV2 safety, with the potential for timely identification of emerging safety concerns and provides an overview of global trends of AEFIs reported post nOPV2.
    b. Members recommended that efforts must be undertaken to improve timeliness and completeness of safety data reported to Vigibase.
    c. The sub-committee members agreed that the WHO vaccine pharmacovigilance and WHO regional offices team should continue to review Vigibase data and jointly discuss with GPEI on twice-annual basis for a 1-year period after prequalification. At the same time the GPEI should adopt a proactive approach towards informing the WHO global and regional pharmacovigilance teams regarding any cluster or significant safety event identified through AFP surveillance systems. Efforts for better integration of AEFI and AFP

surveillance systems will complement ongoing efforts to strengthen vaccine pharmacovigilance and assure public confidence in vaccines.

11. The sub-committee members acknowledged that the multi-country initiative for monitoring nOPV2 safety during the EUL period has helped strengthen vaccine safety monitoring systems and contributed to improved understanding regarding the current status of vaccine pharmacovigilance capacity in resource constrained settings, whilst highlighting several areas for further improvement, including timeliness and completeness of clinical information and vaccine exposure data collected, as well as capacity for conducting causality assessments by respective NECs. They recommended that lessons learned from this initiative should be encapsulated in manuscripts towards informing future strategies for strengthening vaccine pharmacovigilance in LMICs. The sub-committee also recommended that key discussions and conclusions from this final meeting are reported to appropriate advisory bodies including the Strategic Advisory Group of Experts (SAGE) on immunization and the GACVS at subsequent meetings for wider dissemination of the actionable insights and recommendations gleaned from this initiative.
12. The sub-committee members concluded that, with nearly 1 billion 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 adverse event reports, either temporally or geographically, that would give rise to any unexpected safety concerns.

The sub-committee members applauded the experts and secretariat for their diligent and comprehensive, timely reports and conducting the meetings efficiently. The meeting concluded with a vote of thanks from the secretariat, acknowledging the sub-committee's extensive time and efforts in comprehensively reviewing the safety of the nOPV2 during the EUL period.