GACVS SUB-COMMITTEE ON NOVEL OPV2 SAFETY

20th January 2021

First Meeting

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Opening note by Aidan O'Leary:

The opening note by Aiden highlighted the status quo of the polio eradication program including the 15% increase in type 2 circulating derived poliovirus (cVDPD2) outbreaks reported between 2019 and 2020 in the African region of WHO. The importance of novel OPV2 to address type 2 outbreaks was emphasized. nOPV2 was authorized for use under Emergency Use Listing (EUL) by the WHO prequalification (PQ) team in November 2020. This is the first vaccine granted EUL by WHO PQ and will be implemented under specific EUL conditions and protocols during 2021. As such, monitoring of safety events will be critical to ensure maximal acceptance and safety. Should the safety and efficacy data indicate, nOPV2 will be the vaccine for choice in the future for outbreak response.

Polio update, epidemiology, and rationale for nOPV2 by Ondrej Mach:

Ondrej provided a background on the status of wild poliovirus (WPV) and cVDPV worldwide. Although WPV2 and WPV3 were certified eradicated in 1999 and 2012 respectively, WPV1 transmission continues to be endemic in Afghanistan and Pakistan. Following the removal of type 2 component from trivalent oral poliovirus vaccine (tOPV) in 2016, it was anticipated that paralytic cases due to cVDPV2 would be eliminated within 2 years. However there have been an increasing number of paralytic cases worldwide due to cVDPV2 compared to WPV1 (904 cVDPV2 and 140 in 2020).

Currently type 2 monovalent OPV (mOPV2) is used in cVDPV2 outbreak response; in the event that vaccine coverage during outbreak response is sub-optimal, there is a small risk of seeding new outbreaks. nOPV2 was developed to be more genetically stable and has comparable immunogenicity to mOPV2. As such should safety and Phase III data indicate, nOPV2 would be the vaccine of choice for cVDPV2 outbreaks in the future.

Overview of nOPV2 working group, nOPV2 clinical development and country readiness by Simona Zipursky, Ananda Bandyopadhay:

Ananda provided an overview to the nOPV2 working group and its focus areas. The core working group is co-chaired by WHO and BMGF and oversees the work in focus areas by sub-groups which include the: initial use country support sub-group, research, data analysis and modeling sub-group, manufacturer support sub-group, genetic characterization sub-group. The WG also coordinates with additional groups in the areas of vaccine supply, communications and country readiness verification. Key resources can be found on: www.polioeradication.org/nOPV2.

Background on the clinical development of nOPV2 was provided:

- nOPV2 is a modification of the currently used mOPV2 vaccine
- nOPV2 is less likely to revert to a form that can cause paralysis as it is more genetically stable; which reduces the risk of seeding new cVDPV2 outbreaks, compared to mOPV2
- Phase II infant studies (which used mOPV2 as historical control):
    - did not identify any safety signals, neither SAEs related to nOPV2 use
    - demonstrated comparable immunogenicity (seroconversion rates)
    - demonstrated comparable duration and extent of viral shedding for nOPV2

Future planned clinical studies were outlined, including Phase III, birth dose immunogenicity study, observational pregnancy study, primary immunodeficiency study / iVDPV registry, seroprevalence study post implementation, and immunogenicity study following concomitant administration of nOPV2 with bOPV. The EUL process and preparations for nOPV2 rollout were outlined specifically focusing on the criteria for initial use criteria under EUL which was endorsed by SAFE in April 2020. Given the stringent readiness criteria which countries are required to meet, it was highlighted that any country interested in using nOPV2 in the next 3-6 months should begin preparations for nOPV2 without delay. Furthermore, countries identified as being high risk for VDPV2 detection and outbreaks have been identified and work has already commenced to strengthen their capacity to prepare for nOPV2 use.

Questions for clarification

- Superiority design is used to compare genetic stability of nOPV2, with analysis ongoing (full data set is not yet available)
- nOPV2 will be used only for outbreak purposes under EUL (NOT in routine immunization) and as such, individual informed consent will not be needed
- Countries are to meet specific readiness criteria for initial use of nOPV2 under EUL, which include demonstrating the capacity in the following areas: to detect VDPV2 through environmental surveillance (ES); acquire and distribute vaccine in a timely manner; monitoring and surveillance on AE, safety and AFP.
- During the initial use phase, nOPV2 should be used alone for outbreak response, to avoid interference with other polio vaccines in initial use there will be a period of 6 weeks since the last use of bOPV2 prior to using nOPV2 in the area to avoid recombination
- WHO PQ team was engaged to identify the regulatory agencies of the countries identified as high risk for VDPV2 detection and outbreaks
- Target age group will be 0-5 years (typical for polio outbreaks)
- Effectiveness in controlling cVDPV2 outbreaks will be determined studies involving immunogenicity - case control and seroprevalence studies; however the scope work for this sub-committee will be on safety monitoring

Safety monitoring requirements under EUL, by Martin Eisenhawer:

Martin provided an overview on the EUL mechanism and the safety monitoring requirements from WHO PQ expected of the Global Polio Eradication Initiative (GPEI) and the vaccine manufacturer Biofarma. Requirements from WHO PQ include the establishment of a risk management plan (established), pharmacovigilance plan (established), and the monitoring of persons at high risk including PID and pregnant women (concept note currently under review by PQ). Specific details on the commitments and reporting timeframes expected from the GPEI and from countries where nOPV2 will be used were outlined, including:

- AFP surveillance
- ES Surveillance
- AESI surveillance
- iVPV registry
- Pregnancy registry
- PID surveillance

It was clarified that countries which use nOPV2 in the initial use phase under EUL will be required to meet specific country criteria including:

- NPAFP rate ≥ 2 per year per 100,000 aged under 15 years at national level
- Stool specimen collection ≥ 80% of AFP cases (2 specimens collected ≥ 24 hrs apart, within 14 days of paralysis, with arrival of specimens in a WHO accredited laboratory with reverse cold chain maintained in good condition)
- Identification of enteroviruses in at least 50% of environmental samples in a one-year period
- Establishing a national safety / causality committee
- Annual AEFI rate over WHO minimum standard of >10 per 100,000 surviving infants
- Active AFP surveillance
- Enhanced ES (at least one functional ES site with sensitivity to detect EV in at least 50% samples over 6 mos in areas where nOPV2 will be used)

Points for clarification

- Phase III clinical trials have not yet been conducted. Other than studies outlined in presentation 3,4,5 (which include field and observational studies including for special populations, as well as seroprevalence studies), there are no other planned clinical trials. For any new clinical trials these would be categorized as Phase II, dependent on the design of these studies and the participating country's regulatory agency's classification of the phase of the study.
- There are 2 uses of nOPV2 – restricted use in studies (one study ongoing in Bangladesh) and in mass vaccination campaigns / supplementary immunization activities / SIAs, for outbreak response.
- The 6week period between nOPV2 use and mOPV2 use only applies to the initial use phase and only for the specific area where nOPV2 will be used.
- The scope of the nOPV2 response will be determined by risk assessment conducted by one of the GPEI groups. There may be situations where a national campaign might be warranted. In other countries the scope may be limited to specific sub-national areas.
- The current commitment is that at least one functional ES site needs to be present. In case an ES site is not present in an outbreak area where the use of nOPV2 is considered, it either needs to be established or initial use will not be possible for this outbreak
- It was highlighted that there needs to be further clarity on the roles and ToRs on the below committees, given the potential overlap between AFP and AEFI surveillance, specifically -
    - National AEFI committee reviewing AEFI data and
    - National committee reviewing the AFP data

Field data collection for AEFI and AESI by Zunera Gilani

Zunera emphasized that post-licensure safety monitoring is critical to detect rare or unexpected adverse events. Given that nOPV2 is being introduced relatively quickly and prior to Phase III results or licensure, enhanced safety surveillance will be imperative to ensure robust data are available for decision making in the setting where data may be limited.

For nOPV2 AEFI data will be collected using already established country protocols and staff with support provided by GPEI (passive AEFI safety surveillance). Given the limitations of passive AEFI surveillance,

during the EUL period, active AESI surveillance will also be conducted using standard protocols adapted to the country context by trained surveillance staff; with AESI surveillance visits combined with AFP and AEFI visits. Definitions of the AESIs, AESI surveillance activities, and data flow were outlined. The AESI case ascertainment and data abstraction forms were presented and it was clarified that where possible, an ODK data collection platform would be used.

Points for clarification

- It was clarified that one limitation of gathering prospective comparative AESI data (for a period of 6 months prior to nOPV2 use), is that at present, the specific countries where nOPV2 will be used have not yet been confirmed and data quality may be poor.
- The impact of COVID on AESI surveillance is not yet well defined, as COVID vaccination activities may be occurring at the same time. Careful planning of surveillance visits will therefore be important to ensure appropriate timing of dedicated AESI visits without compromising COVID efforts and safety of personnel.
- Countries under consideration for nOPV2 initial use include Liberia, Congo, Nigeria and Benin.
- As there are limitations on acquiring background rates for AESIs, gathering the 6month retrospective data will be important. This can be modified to 12 months should there be a lack of retrospective records / data.
- It was clarified that although active surveillance is very resource intensive it is required throughout the EUL period as a condition of nOPV2 use under EUL.
- As the conditions for nOPV2 use under EUL are different than for COVID19 (as timing for vaccination activities may differ), it is not clear if it will be possible to use the same active surveillance sites or resources for COVID 19 surveillance.
- It was clarified that hospital data will be summarized including deaths (even if this generates more data without a comparison group), as there should be some historical data available.
- It was highlighted that AESI data flow and processing will need to be reviewed and adapted as per the needs of the programmatic needs and country-specific conditions

The genetic stability sub-group and genetic stability related data by Javier Martin:

Javier provided background on nOPV2 development from genetic stability perspective highlighting that nOPV2 had favorable safety profile, comparable immunogenicity and shedding profile compared to mOPV2; and that current data support the view that nOPV2 has a significantly lower risk of paralysis in humans, compared to mOPV2.

The scope of work of the genetic characterization sub-group, the data and information flow with timelines, and, the diagnostic algorithm of samples from AFP cases and environmental samples were outlined.

The temperature stability, genetic and molecular structure of the nOPV2 candidates were presented. Details of the specific parameters to monitor nOPV2 genetic stability were presented, including presence of nOPV2 genetic modifications to confirm that the virus isolate was derived from nOPV2; and testing focused on speficic mutations with potential to reduce genetic stability and / or increased neurovirulence / transmissibility (e.g. reversion at Sabin 2 attenuation site at VP1-143, recombination with human enterovirus in 5'NCR replacing Domain V, etc).

Points for clarification

- Genetic stability is determined by checking to whether there are specific genetic changes. It was clarified that every isolate will be fully sequenced and that should there be any concerns, follow up will ensure.
- During initial use phase, reporting will occur monthly; in the wider use phase, the frequency of reporting will need to be determined.
- Regarding the timeframe for virus characterization and sequencing, this would depend on the review of the case and be specific to that case, taking into account multiple factors including virus drift from the original form, whether the virus is replicating
- Currently testing is ongoing and although there is no direct evidence yet regarding IPV effectiveness against nOPV2 virus, it is expected that IPV would be effective.
- In the case a new mutation which is more virulent evolves (standalone or due to recombination), there would have to be contingency plan.
- nOPV2 behavior in immunocompromised individuals has not yet been studied, however studies and a registry are planned for those with PID.
- Answer: Overall to date, approximately 20,000 stool samples have been tested for virus detection/characterization across different studies. Among these samples, a pre-defined, select sub-set of samples ("Exploratory Endpoint Specimen"/EES) that fits criteria related to amount of virus in stool have been further tested (post amplification of viruses) for next generation sequencing (NGS); this process is defined in a way to ensure that samples with a higher likelihood of reversion are selected and with this, roughly 100 samples have been analyzed by NGS to generate data on genetic stability with further testing on-going.

Safety data flow for the GACVS sub-committee, and workings of the sub-committee by Grace Ruth Macklin, Carolyn Sein:

The AEFI, AESI, AFP and ES data work flow from country to regional to global level were outlined with clarification of the scope of work of various groups in the work flow.

It was clarified that the scope of work of GACVS sub-committee will be to

- Review the report of safety outcomes for the entire EUL period (~18 mo after implementation)*
    - On a monthly basis during the initial use phase
    - On a 3monthly basis after the initial use phase (wider use phase until the end of EUL)
- Meet after each outbreak response mass vaccination campaign
    - Day 42 + 7 d after round 1
    - Day 72 + 7 d

  } 12-13 wks after first round
- Advise from a safety perspective, whether to move from initial to wider use under EUL
- Meet on an ad-hoc basis should SAE be reported

*All reports / analysis will be prepared by CDC and P95 in the initial use phase; and by P95 in the wider use phase

Annex 1

First meeting of the GACVS sub-committee on nOPV2 safety

Date: 20 January 2021

Time: 1400-1750 GVA / CET

Location: virtually through Microsoft Teams

Co-Secretariats: Carolyn Sein (POL, WHO); Madhav Balakrishnan (PVG, WHO)

Co-chairs: DS Akram (GACVS), Peter Wright (DSMB WHO POL Clinical trials)

	Session	**Presenter / participants**
1400-1410	Welcome and introduction	WHO POL Dir Aiden O'Leary
1410-1420	Polio landscape and rationale for nOPV2 development	WHO POL Ondrej Mach
1420-1430	Overview of GACVS sub-committee	WHO POL Secretariat
1430-1450	Introduction to the nOPV2 WG	nOPV2 WG Ananda Bandyopadhyay / Simona Zipursky
1450-1510	nOPV2 development and clinical trials	nOPV2 WG Ananda Bandyopadhyay
1510-1530	nOPV2 country readiness and roll out under EUL	WHO POL Ananda Bandyopadhyay (on behalf of Simona Zipursky)
1530-1550	nOPV2 safety monitoring commitments under EUL	WHO POL Martin Eisenhawer
1550-1610	Discussion - Objective: • Understand polio & nOPV2 landscape; EUL process • Biofarma in attendance to answer any queries	All
1610-1620	Break	
1620-1640	Field data collection for AEFI, AESI	CDC Zunera Gilani
1640-1700	Introduction to the Genetic Stability SG and genetic stability related data	Genetic Characterisation Sub-Group Javier Martin
1700-1720	GACVS sub-committee – composition & scope of work - Data flow and timelines - ToRs - roles, responsibilities - P95: epi & pharmacovigilance consultant support	Secretariat / Grace Macklin
1720-1740	Discussion - Objective: • Understand working arrangements	All
1740-1750	Wrap up	WHO POL / Secretariat

Annex 2

Role	Institution	Name	Contact
Expert members	GACVS	Rita Helfand NK Arora DS Akram	rzh7@cdc.gov nkarora@inclentrust.org dsakram@gmail.com
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