TANZANIA NATIONAL IMMUNIZATION TECHNICAL ADVISORY GROUP

Recommendation on nOPV2 vaccine

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Executive summary

I. Introduction

a. Poliomyelitis (polio) and Polio Vaccines

Poliomyelitis (polio) is a highly infectious disease caused by a virus that can invade the nervous system and cause permanent paralysis. The number of polio cases per year has dropped by more than 99 percent since the inception of the Global Polio Eradication Initiative (GPEI) in 1988; wild polio types 2 and 3 have been eradicated; and in late summer 2020, the WHO African Region was certificated wild polio-free [1].

Globally, Polio remains endemic in two countries – Afghanistan and Pakistan (Wild Poliovirus type 1). Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio [2]. The circulating vaccine-derived poliovirus type 2 (cVDPV2) has been confirmed in Uganda[3] and recently the Africa has reported a case of wild polio in Malawi after being declared free of indigenous wild polio in August 2020[4].

Improvements in hygiene and sanitation have helped minimize exposure to the polio virus and thus the number of polio cases, but the only way to truly prevent the disease is through vaccination.

Inactivated polio vaccines (IPV) and oral polio vaccines (OPV) have propelled us to historically low levels of polio incidence, but new tools are needed for the last mile of disease eradication. OPV is highly effective in high-burden regions and during disease outbreaks because it protects the individual and halts person-to-person disease transmission. However, on very rare occasions in under-immunized populations, the live, attenuated (weakened) virus used in OPV can mutate and circulate in a community. This is known as circulating vaccine-derived poliovirus (cVDPV). cVDPVs that develop from the ongoing, necessary use of currently available OPV add a complicating factor to ending polio transmission for good, due to the potential of cVDPVs to cause future outbreaks. However, if a population is fully immunized, they will be protected against both vaccine- derived and wild polioviruses.

IPV is highly effective at preventing disease and does not carry the risk of generating cVDPVs, but it does not confer the same type of immunity that prevents person-to-person transmission, necessary in

[1] nOPV-Fact-Jan2021 NITAG.pdf
[2] https://polioeradication.org/ accessed on 24th February 2022
[3] https://polioeradication.org/uganda/ accessed 27th February 2022
[4] https://www.afro.who.int/news/malawi-declares-polio-outbreak/accessed 27th February 2022

controlling outbreaks. It is also much more expensive than OPV and more difficult for untrained health workers to deliver in settings where the vaccines are needed most.

To stamp out the last pockets of wild and vaccine-derived polio and protect against potential outbreaks, immunization partners are advancing novel oral polio vaccine candidates (nOPVs) against poliovirus types 1, 2, and 3. Like the currently available OPVs, the nOPV candidates are designed to prevent person-to-person disease transmission, without carrying the same risk of seeding new vaccine-derived polio cases. Since the attenuated (weakened) type 2 strain in the currently available OPV causes the majority of cVDPV outbreaks, the program advanced research on nOPV2 first.

Based on promising Phase I and II clinical trial data, and on the urgent need to address cVDPV2 outbreaks, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on immunization endorsed the nOPV2 Working Group's framework for initial use of nOPV2 under WHO's Emergency Use Listing (EUL) procedure. The EUL involves careful and rigorous analysis of available data to enable early, targeted use of yet-to-be licensed products for a Public Health Emergency of International Concern, which polio has been since 2014 [1].

b. General information on the novel Oral Polio Vaccine type 2(nOPV2)

The novel oral polio vaccine type 2 (nOPV2) is a modified version of the existing monovalent oral polio type 2 vaccine (mOPV2, also known as Sabin OPV2). As nOPV2 has been shown in studies to provide comparable protection to mOPV2 against type 2 poliovirus while being less likely to lead to cVDPV2. nOPV2 has received a recommendation for use through the Emergency Use Listing procedure (EUL) of the World Health Organization (WHO) [5]. It is supplied in 5ml glass vial with a dropper, with each vial containing 50 doses, with 10-vial packs. The volume per dose is 0.55cm^3 or 27.5 cm^3 per vial with expected wastage factor for a 50-dose vial is 1.33 (wastage rate = 25%). The nOPV2 is not affected by freezing and thawing cycles or events [6].

[5] nOPV2-Overview-Guidance.pdf
[6] nOPV2-vaccine-handling.pdf

Figure 1:novel Oral Polio Vaccine 2 (nOPV 2) package

II. Methodology

a. Establishment of a working group

The Tanzania Immunization Technical Advisory Group (TITAG) held its 5th meeting from 21st to 26th February 2022 in Dodoma to address the policy question ***"Should nOPV2 be introduced to Tanzania populace in response to Polio outbreak? "What are the implications both technically and programmatically?*** **(Appendix I)**. To answer the research question posed by the Ministry of Health, TITAG members used their usual three working groups. The first group was assigned to work on the disease burden, characteristics of the nOPV2 , safety, efficacy and efficiency; the second group focused on the economical cost of introducing the vaccine; and the third group focused on the on programmatic and delivery strategies.

Members used a scientific and systematic approach to review evidence. Members used the programmatic perspective as well as the background of the disease that was provided by the Secretariat. To make the process effective, each member was assigned a section to work on and present to members for discussion and deliberation.

b. Recommendation framework

The groups reviewed the epidemiology of the disease and the potential use of vaccine in particular nOPV 2 during Polio outbreak. In addition, members considered the burden of the disease, vaccine effectiveness and safety as well as cost-benefit criteria, and values and preferences, acceptability, feasibility, and equity for the vaccine use. The TITAG subgroup members used the GRADE approach to assess the certainty of evidence from low to high certainity.

c. Evidence search and assessment

Articles and reports from WHO were included if they provided data on nOPV 2 vaccine involving human subjects, reported primary data, data relevant to the efficacy and safety outcomes being measured, and included data for the specific vaccine formulation and dosage, and schedule being recommended.

III. Presentation of the evidence

a. Vaccine and immunization characteristics

i. Safety

Novel OPV2 has demonstrated a favorable safety profile and immunogenity in phase I and II clinical trials in infants, children and adults which warranted a WHO emergency use listing.

ii. Type, consequences and frequency of short- & long-term adverse events

A phase I double blinded trial among healthy adults aged 10-50 years conducted to evaluate safety and immunogenity of nOPV2 compared to mOPV2. Safety data from this trial showed that severe events were reported in 6(40%) in nOPV2 vaccine candidate. Most of these events were increased blood creatinine phosphokinase but were not accompanied by clinical signs. Other events were increased aspartate aminotransferase, headache and diarrhea. Most of events resolved spontaneously. Additionally, no serious adverse event occurred during the study[7].

Results from two randomized phase II controlled studies to evaluate safety and immunogenicity of novel OPV2 vaccines and monovalent OPVC2 vaccine among healthy adults aged 18-50 years of age, reported the most frequent adverse events to be headache, fatigue, abdominal pain, diarrhea, and myalgia, with no difference in frequency or severity across groups [8]. Moreover, the original suspicion that elevated blood phosphokinase and aspartate aminotransferase was due to excessive exercise by the affected participants living in containment appears to be confirmed, as grade 3 or 4 increases were rare and no consistent

[7] Van Damme, P., De Coster, I., Bandyopadhyay, A. S., Revets, H., Withanage, K., De Smedt, P., ... & Gast, C. (2019). The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. The Lancet, 394(10193), 148-158

[8] De Coster I, Leroux-Roels I, Bandyopadhyay AS, Gast C, Withanage K, Steenackers K, De Smedt P, Aerssens A, Leroux-Roels G, Oberste MS, Konopka-Anstadt JL. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials. The Lancet. 2021 Jan 2;397(10268):39-50.

changes were observed in this larger novel OPV2 study. All vaccines appeared safe; no definitely vaccine-related withdrawals or serious adverse events were reported.

A two single-centre, multi-site, partly-masked, phase II randomized trials was conducted in healthy cohorts of children (aged 1–4 years) and infants (aged 18–22 weeks) in Panama to assess safety and immunogenicity of the two novel OPV candidates compared with a monovalent Sabin OPV in children and infant. A total of 684 participants were enrolled. In this trial, three participants developed SAEs with subsequent admission (pneumonia in monovalent OPV2, mild bronchitis 13 days after a second-high dose of novel OPV2-c1, and a soft tissue preauricular abscess 24 days after receiving high-dose novel OPV2-c2). None was causally associated with the vaccines. Most solicited adverse events, mainly consisted of transient loss of appetite, abnormal pain, excessive crying, irritability, fever, and diarrhea. These events were described as mild with few individuals having adverse events described as severe. Vaccinations were safe and well tolerated with no causally associated serious adverse events or important medical events in any group [9].

Data from these clinical studies show nOPV2 to be well tolerated in adults, young children, and infants, with no indication of any increase in general safety risk compared to mOPV2. Details of these studies are described in Appendix II. Phase III studies are still ongoing; therefore, preliminary results are not yet published.

Additionally, safety data showed that among 111,989,393 doses of nOPV2 distributed in Nigeria, Sierra Leone, Benin, Liberia, Congo Brazzaville and Tajikistan from March 2021 to November 2021, have shown no evidence of any specific clusters or patterns of AEFI/AESI of safety concern. For the 88,140,212 doses administered in Nigeria, 3 reports of suspected VAPP have been identified so far through surveillance in Nigeria, and judged by the National Experts Causality committees (NEC) as being consistent with a causal association, the reporting rate of 0.007/100,000 vaccines in Nigeria is below the

[9] Sáez-Llorens X, Bandyopadhyay AS, Gast C, De Leon T, DeAntonio R, Jimeno J, Caballero MI, Aguirre G, Oberste MS, Weldon WC, Konopka-Anstadt JL. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials. The Lancet. 2021 Jan 2;397(10268):27-38.

expected range of VAPP associated with mOPV2 vaccine of 0.025-0.4/100,000 vaccines, and therefore would not indicate an unexpected safety concern.

The other three(3) AEFI/AESI reports judged by the Nigeria national causality committees to be consistent with a causal association (anaphylaxis, allergic reaction and meningo-encephalitis) do not generate any new safety signals. The national causality committees in Congo, Benin, Liberia and Tajikistan have found no AEFI/AESI cases to be consistent with a causal association with nOPV2 [10].

- **Risk factors that can lead to adverse events**

No specific risk factors for adverse events were identified in phase I and II studies

- **Contraindications to vaccination**

Novel OPV2 is contraindicated in pregnant women and in those with primary immune deficiency disease or suppressed immune response from medication, leukaemia, lymphoma or generalized malignancy [11].

iii. Efficacy and effectiveness

- **Type-specific protection afforded**

Humoral response is elicited in mice and humans following immunization with nOVP2, at comparable levels with that of Sabin2. The initial evaluation of nOPV2 immunogenicity was carried out in susceptible transgenic mice infected intraperitoneally with dilutions of Sabin2 or nOPV2 followed by collection of sera at 21 days post-inoculation and tested by neutralization (NT) assay to determine antibody titers [12]. Inoculation with Sabin2 tended to induce higher geometric mean titers of neutralizing antibodies, particularly at low doses. However, the difference between antibody titers induced by Sabin2 and nOPV2 at the tested doses and at the tested sample size did ot reach statistical significance. Importantly, Sabin2 and nOPV2 had similar seroconversion rates, 75%–100% of vaccinated mice generated neutralizing antibodies at the tested doses with a single immunization. Hence the immunogenicity of nOPV2 was not significantly inferior to that of Sabin2. Additional experiments in humans will be required to further establish the immunogenic capacity of nOPV2.

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[10] nOPV2 vaccine safety-end of EUL initial use period report, 13 March 2021-24November 2021

[11]Rrecommendation for an emergency use listing (eul) of novel oral polio vaccine type 2 (nopv2) submitted by Biofarma (persero). Published on: 01 December 2020

[12] Yeh MT, Bujaki E, Dolan PT, Smith M, Wahid R, Konz J, Weiner AJ, Bandyopadhyay AS, Van Damme P, De Coster I, Revets H, Macadam A, Andino R. Engineering the Live-Attenuated Polio Vaccine to Prevent Reversion to Virulence. Cell Host Microbe. 2020 May 13;27(5):736-751.e8. doi: 10.1016/j.chom.2020.04.003.

A blinded phase 1 trial was conducted in Belgium involving healthy adults (aged 18–50 years) previously immunized exclusively with inactivated poliovirus vaccine were administered a single dose of nOPV2 S2/cre5/S15domV/rec1/hifi3 (n = 15) and isolated for 28 days in a purpose-built containment facility[13]. Using stool samples collected near days 0, 14, 21, and 28, evaluation on intestinal neutralization and immunoglobulin A responses to the nOPV2s was done and found that nOPV2 induced detectable poliovirus type 2–specific intestinal neutralizing responses in 40.0% of participants.

A randomized clinical phase 2 study involving healthy adults aged 18–50 years with documented history of at least three polio vaccinations, including OPV in the phase 4 study and either OPV or inactivated poliovirus vaccine (IPV) in the novel OPV2 phase 2 study, with no dose within 12 months of study start was carried out[14]. Novel OPV2 was found to be immunogenic as monovalent OPV2 in previously OPV-vaccinated and IPV-vaccinated adults. These data supported the further assessment of the vaccine candidates in children and infants.

In a two single-centre, multi-site, partly-masked, randomised trials in healthy cohorts of children (aged 1–4 years) and infants (aged 18–22 weeks) in Panama: a control phase 4 study with monovalent Sabin OPV2 before global cessation of monovalent OPV2 use, and A phase 2 single-centre, multi-site, partly-masked, randomised trials in healthy cohorts of children (aged 1–4 years) and infants (aged 18–22 weeks) study with low and high doses of novel OPV2 candidates administered with two doses 28 days apart[15]. Nearly all children were seroprotected at baseline, indicating high baseline immunity. In children, the seroprotection rate 28 days after one dose was 100% for monovalent OPV2 and both novel OPV2

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[13] Brickley EB, Connor RI, Wieland-Alter W, Weiner JA, Ackerman ME, Arita M, Gast C, De Coster I, Van Damme P, Bandyopadhyay AS, Wright PF. Intestinal antibody responses to two novel live attenuated type 2 oral poliovirus vaccines in healthy adults in Belgium. J Infect Dis. 2020 Dec 24:jiaa783. doi: 10.1093/infdis/jiaa783.

[14] De Coster I, Leroux-Roels I, Bandyopadhyay AS, Gast C, Withanage K, Steenackers K, De Smedt P, Aerssens A, Leroux-Roels G, Oberste MS, Konopka-Anstadt JL, Weldon WC, Fix A, Konz J, Wahid R, Modlin J, Clemens R, Costa Clemens SA, Bachtiar NS, Van Damme P. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials. Lancet. 2021 Jan 2;397(10268):39-50. doi: 10.1016/S0140-6736(20)32541-1.

[15] Sáez-Llorens X, Bandyopadhyay AS, Gast C, Leon T, DeAntonio R, Jimeno J, Caballero MI, Aguirre G, Oberste MS, Weldon WC, Konopka-Anstadt JL, Modlin J, Bachtiar NS, Fix A, Konz J, Clemens R, Costa Clemens SA, Rüttimann R. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials. Lancet. 2021 Jan 2;397(10268):27-38. doi: 10.1016/S0140-6736(20)32540-X.

candidates. In infants at day 28, 91 (94% [95% CI 87–98]) of 97 were seroprotected after receiving monovalent OPV2, 134 (94% [88–97]) of 143 after high-dose novel OPV2-c1, 122 (93% [87–97]) of 131 after low-dose novel OPV2-c1, 138 (95% [90–98]) of 146 after high-dose novel OPV2-c2, and 115 (91% [84–95]) of 127 after low-dose novel OPV2-c2. Non-inferiority was shown for low-dose and high-dose novel OPV2-c1 and high-dose novel OPV2-c2 despite monovalent OPV2 recipients having higher baseline immunity.

In a double-blind, single-centre phase 1 trial, participants were isolated participants in a purpose-built containment facility at the University of Antwerp Hospital (Antwerp, Belgium), to minimise the risk of environmental release of the novel OPV2 candidates. Participants, who were recruited by local advertising, were adults (aged 18-50 years) in good health who had previously been vaccinated with IPV, and who would not have any contact with immunosuppressed or unvaccinated people for the duration of faecal shedding at the end of the study[16]. The novel OPV2 candidate was immunogenic and increased the median blood titre of serum neutralising antibodies; all participants were seroprotected after vaccination.

Critical determinants of the immune response

Poliovirus particles form two distinct antigenic structures: the native D-antigen associated with mature infectious virus and the non-native C-antigen[17]. The D-antigen elicits protective immune responses but can be converted to the C-antigenic form, for example by heating[18]. The C-antigen is conformationally expanded and does not induce long-lasting immune protection, making it unsuitable as a vaccine [19]. Like Sabin-2, nOPV2 is shed in stool, and possibly saliva of vaccine recipients. Transmission of vaccine virus to close contacts is possible and is likely to be nogreater and possibly less than that of Sabin-2. This vaccine should be used with caution in close contacts of persons with immune deficiency disorder. If

[16] Van Damme P, De Coster I, Bandyopadhyay AS et al . The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. Lancet. 2019 Jul 13;394(10193):148-158. doi: 10.1016/S0140-6736(19)31279-6. Epub 2019 Jun 4. PMID: 31174831; PMCID: PMC6626986.

[17] HUMMELER K, HAMPARIAN VV. Studies on the complement fixing antigens of poliomyelitis. I. Demonstration of type and group specific antigens in native and heated viral preparations. J Immunol. 1958 Dec;81(6):499-505.

[18] Le Bouvier, G. L. The modification of poliovirus antigens by heat and ultraviolet light. Lancet 269, 1013–1016 (1955).

[19] Strauss, M., Schotte, L., Karunatilaka, K. S., Filman, D. J. & Hogle, J. M. Cryo-electron microscopy structures of expanded poliovirus with VHHs sample the conformational repertoire of the expanded state. J. Virol. 91, https://doi.org/10.1128/JVI.01443-16

contact must occur, precautions should be taken to avoid contact with stool or saliva of the vaccinated individual.

The vaccine is contraindicated in those with primary immune deficiency disease or suppressed immune response from medication, leukaemia, lymphoma or generalized malignancies.

- **Clinical Vaccine Efficacy and Effectiveness**

The available evidence suggests that nOPV2 (the first new OPV vaccines in over 50 years) could be associated with less paralytic (polio) disease and potentially a lower risk of leading to new outbreaks including reversion to viral virulence. This has been reported to be due to the superior genetic and phenotypic stability of nOPV2 strains compared to Sabin-2 strains that were subsequently shed from children aged 1 to 5 years, a key target age group for potential outbreaks[20,23]. However, there is still no reported direct quantitative means to establish the reduced risk of paralysis in human given that there are no larger studies and respective longtudinal data in the real world settings to verify this suggestion.

Noticeably, preclinical models of nOPV2 candidates have been reported to be less transmissible and genetically more stable than the Sabin OPV, and so less likely to revert to neurovirulent strains that are shed from stools of vaccinees[21,22]. The first clinical demonstration of novel OPV vaccine candidates in human volunteers (healthy adults) found that vaccine poliovirus shedding stopped at a median of 12 and 23 days after administration of nOPV2 candidate one and two respectively[23]. However, preliminary analyses of studies in children and infants have shown that the novel OPV2 candidates had lower viral shedding in stools 28 days after vaccination compared to those with monovalent OPV2 in a historical control study[24]. Overall, nOPV2 provides comparable protection against poliovirus type 2 while being more genetically stable less likely to be associated with the emergence of type 2 circulating vaccine-derived poliovirus with a potential to sustainably stop outbreaks compared to the existing OPV2 vaccine[25].

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[20] Wahid et al Evaluating stability of attenuated Sabin and two novel type 2 oral poliovirus vaccines in children. npj Vaccines (2022)7:19 ; https://doi.org/10.1038/s41541-022-00437

[21] Bandyopadhyay AS, Garon J, Seib K, Orenstein WA. Polio vaccination: past, present and future. Future Microbiol. 10(5), 791–808(2015)

[22] Van Damme et al Poliopolis: pushing boundaries of scientific innovations for disease eradication. Future Microbiol. (2019) 14(15), 1321–1330

[23] Van Damme, P., De Coster, I., Bandyopadhyay, A. S., Revets, H., Withanage, K., De Smedt, P., ... & Gast, C. (2019). The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. The Lancet, 394(10193), 148-158

[24] Sáez-Llorens X, Bandyopadhyay AS, Gast C, De Leon T, DeAntonio R, Jimeno J, Caballero MI, Aguirre G, Oberste MS, Weldon WC, Konopka-Anstadt JL. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials. The Lancet. 2021 Jan 2;397(10268):27-38.

[25] Polio Global Eradication Initiative https://polioeradication.org/nopv2/ accessed on 23 Feb 2022

Further investigation is warranted to establish the nature of any detectable changes in regards to potential neurovirulence of shed virus in comparison with the licensed monovalent OPV2[23,24] with the correspondant impact on the polio disease.

Important to note, there are no phase 3 and real world studies to establish respective nOPV2 efficacy and effectiveness toward the eradication of poliomyelitis hence such studies are further recommended thereof.

- **Duration of protection & waning of immunity, if any**

No data is available at the moment on waning of immunity.

- **Interference regarding protection or immunity with other vaccines?**

To the best of our knowledge there is is no publication documenting the interference regarding protection or immunity with other vaccines

iv. Vaccine indirect effect

There is no anticipated negative effect of nOPV2 on antibiotics and antivirals resistance or herd immunity. Additionally, there is no potential population negative impact through change in age of infection for unprotected individuals or emergence of non-vaccine serotypes as the candidate has been proved to be more genetically stable compared to other routinely used oral polio vaccines".

v. Vaccine characteristics

i. Vaccine presentation & formulation

A novel oral polio vaccine type 2 (nOPV2) is the modified inactivated version of the existing type 2 monovalent OPV (mOPV2). This vaccine has increased genetic stability, hence reduced risk of causing outbreak of vaccine derived polio through environmental contamination with subsequent reduction of the risk of vaccine associated paralytic polio (VAPP).

The poliovirus genome: Poliovirus has a positive-sense, single-stranded RNA genome composed up of one major open reading frame encoding a single polyprotein comprising regions P1 (encoding the viral capsid proteins) and P2 and P3 (proteins for proteolytic processing and replication)[26] (Figure 1A). The viral protease precursor 3CD cleaves P1 into the capsid proteins VP0, VP1 and VP3, and encapsidation of the viral RNA to form the mature virion is associated with cleavage of VP0 into VP2 and VP4,

[26] Kitamura N, Semler BL, Rothberg PG, Larsen GR, Adler CJ, Dorner AJ, Emini EA, Hanecak R, Lee JJ, van der Werf S, Anderson CW, Wimmer E. Primary structure, gene organization and polypeptide expression of poliovirus RNA. Nature. 1981 Jun 18;291(5816):547-53. doi: 10.1038/291547a0.

increasing particle stability[27]. Mature virions containing genome are composed of 60 copies each of the VP1-4 protomer; whilst in naturally occurring empty capsids formed during poliovirus morphogenesis VP0 remains uncleaved [28].

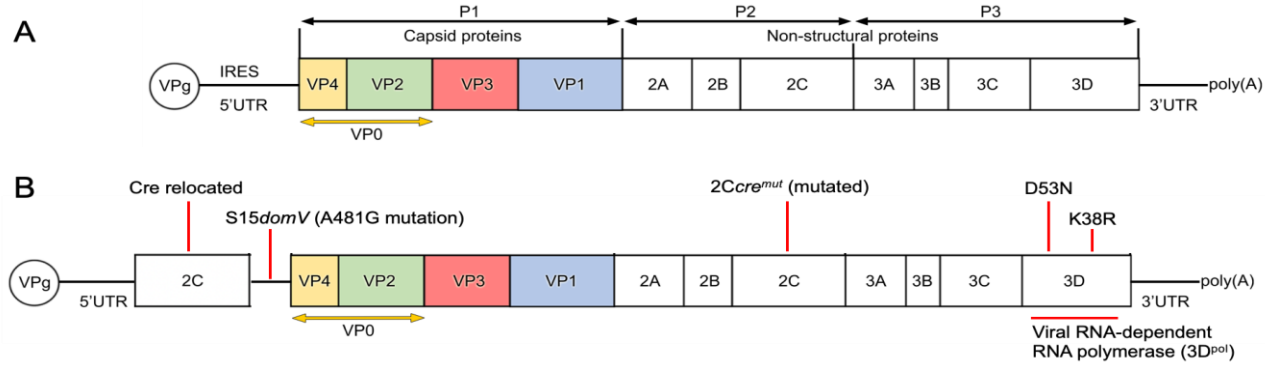

Figure 2 : Schematic representation of the Sabin type 2 (Sabin2) poliovirus[29] and the nOPV2 genomes [30]

The engineered poliovirus type 2 vaccine strain (nOPV2):

Specific genetic modifications within the Sabin type 2 (Sabin2) poliovirus were introduced to develop an engineered live-attenuated oral poliovirus vaccine (nOPV2) with increased genetic stability, slowed Sabin2 virus evolution preventing reversion to virulence while preserving the antigenic and immunogenic characteristics, overall replication strength and thermo-sensitivity characteristics[31]. The resulting nOPV2 is genetically more stable and less likely to regain virulence than the original Sabin2 strain. The genome of nOPV2 polio vaccine candidate carries five modifications of the Sabin2 genome (Figure 1B), including:

a. two modifications within the 5'-untranslated region (5'-UTR) (relocated cis-acting replication element (cre) and S15 domain V (S15domV)) to stabilize attenuation determinants,

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[27] Hindiyeh M, Li QH, Basavappa R, Hogle JM, Chow M. Poliovirus mutants at histidine 195 of VP2 do not cleave VP0 into VP2 and VP4. J Virol. 1999 Nov;73(11):9072-9. doi: 10.1128/JVI.73.11.9072-9079.1999..

[28] Jacobson MF, Baltimore D. Morphogenesis of poliovirus. I. Association of the viral RNA with coat protein. J Mol Biol. 1968 Apr 28;33(2):369-78. doi: 10.1016/0022-2836(68)90195-2.

[29]Bahar MW, Porta C, Fox H, Macadam AJ, Fry EE, Stuart DI. Mammalian expression of virus-like particles as a proof of principle for next generation polio vaccines. NPJ Vaccines. 2021 Jan 8;6(1):5. doi: 10.1038/s41541-020-00267-3.

[30] Yeh MT, Bujaki E, Dolan PT, Smith M, Wahid R, Konz J, Weiner AJ, Bandyopadhyay AS, Van Damme P, De Coster I, Revets H, Macadam A, Andino R. Engineering the Live-Attenuated Polio Vaccine to Prevent Reversion to Virulence. Cell Host Microbe. 2020 May 13;27(5):736-751.e8. doi: 10.1016/j.chom.2020.04.003.

[31] Yeh MT, Bujaki E, Dolan PT, Smith M, Wahid R, Konz J, Weiner AJ, Bandyopadhyay AS, Van Damme P, De Coster I, Revets H, Macadam A, Andino R. Engineering the Live-Attenuated Polio Vaccine to Prevent Reversion to Virulence. Cell Host Microbe. 2020 May 13;27(5):736-751.e8. doi: 10.1016/j.chom.2020.04.003.

b. modifications within 2C coding region by synonymous mutations at eight nucleotide positions in the 2C coding region to inactivate the internal cre in order to prevent recombination, and

c. two mutations in the 3D viral RNA-dependent RNA polymerase (D53N and K38R) to limit viral adaptability. The HiFi, D53N mutation enhances the accuracy of the viral RNA polymerase by increasing the fidelity of replication and the Rec1, K38R reduces the rate of recombination.

Based on these modifications, the novel oral poliomyelitis vaccine is also reffered to as S2/cre5/S15domV/rec1/hifi3. Each of the genetic modifications contribute to genetic stability and attenuation and their combination prevents detectable reversion to neurovirulence by reducing the capacity of the virus to acquire mutations that increase replication fitness in neuronal tissues.

ii. Dosage, schedule & route of administration

The live type 2 novel oral poliomyelitis vaccine (nOPV2 [S2/cre5/S15domV/rec1/hifi3] is a monovalent vaccine containing suspensions of type 2 attenuated poliomyelitis viruses (modified Sabin strains) prepared in Vero cells. Each dose (2 drops = 0.1 mL) contains not less than 10^5 $CCID_{50}$ infective units of type 2 poliovirus. Novel oral poliomyelitis vaccine type 2 (nOPV) must only be administered orally. Two drops (0.1 mL containing not less than 10^5 $CCID_{50}$) are delivered directly into the mouth from the multi-dose vial by a dropper or dispenser.

iii. Possibility of co-administration with other vaccines

Routinely, polio vaccines are co-administered with other childhood vaccines. However, to the best our knowledge, there is no clinical data on the use of nOPV2 with other vaccines .

iv. Flexibility of vaccination schedules

The nOPV2 is indicated for use in outbreak of polio type 2 virus in all age groups and must only be administered orally.

Cold chain & logistic requirements

The vaccine is potent if stored at not higher than -20 C until the expiry date indicated on the vial. It can be stored for up to three months between +2 °C and 8 °C. Once opened, the multi-dose vials should be kept between +2 °C and +8 °C. Multi-dose vials of nOPV2 from which one or more doses of the vaccine have been removed during an immunization session may be used in subsequenct immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met; (i) the expiry date of the vaccine has not passed; (ii) the vaccine vial has been, and will continue tobe, stored atrecommended temperatures; and (iii) the vaccine vial monitor is attached and visible on the vaccine label and is not past its discard point.

The nOPV2 is indicated for active immunization in all groups and must only be administered orally.

b. The disease

i. Burden of disease

Globally, Polio remains endemic in two countries – Afghanistan and Pakistan (Wild Poliovirus type 1). Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio [2].

Circulating vaccine-derived poliovirus continues to be detected in both new and previously affected areas. In 2021, Fourteen non-endemic countries of three Regions, reported total of 326 cases (12 cases due to type 1 and 314 cases due to type 2). While this represents a 70% decline in global cases compared to 2020, the situation remains precarious, with continuing immunity gaps, in particular to type 2 poliovirus, insufficient quality and timeliness of outbreak response and dropping immunization rates related to COVID-19 [32].

Tanzania started to implement Polio Eradication Initiative activities in 1995 based on the strategies and approach developed globally. Prior to 1980 cases of poliomyelitis were occurring but not formally documented. Available statistics indicate that the history of polio disease in Tanzania goes back to 1980 when confirmation of poliomyelitis was based on clinical diagnosis. A total of 1,536 cases were clinically confirmed from 1980 to 1994. The largest epidemic was noted between 1986 and 1988 during which a total of 1,112 cases were recorded.

Following commencement of case-based AFP surveillance and laboratory confirmation of cases in 1995, three virologically confirmed cases of wild poliovirus type 1 were found in Mbeya (1) and Dodoma (2) regions the same year. In July 1996, three more virologically confirmed cases of wild poliovirus type 1 were found in Arusha, Kigoma and Mtwara regions. The last reported indigenous wild poliovirus case in Tanzania was in 1996, a male child aged three years, who had received only one dose of OPV.

Tanzania continued with Country wide AFP surveillance and maintained sensitive surveillance and achieved target indicators.

However, cases of circulating vaccine derived Polioviruses continue to be isolated from almost all Countries bordering Tanzania including Democratic Republic of Congo (DRC), Zambia, Mozambique, Kenya and Uganda. Preparedness and response to Polio outbreaks due to both wild poliovirus and vaccine derived poliovirus type 2(cVDPV2) is important to interrupt transmission and spread of Poliovirus in the

[32] AFP Surveillance IVD Report 2021

Country [33].

c. Economic operational considerations

Polio eradication initiatives started as early as in 1988 when the forty first world health assembly (WHA) sat in Geneva, from 2 to 13 May and came up with resolution WHA 41.8 for global polio eradication by the year 2000 [34]. The milestones for poliomyelitis eradication were initially revised in 2002 and further later in 2012 to accommodate unexpected challenges which were met on the implementation process [35]. Following the revision of milestones, tremendous efforts towards polio eradication were made. Even though for the past 30 years ago, the incidence of polio has dropped by more than 99.99%, from about 350,000 cases a year in 125 countries. There were 175 paralytic wild polio-virus type 1(WPV1) in 2019 from Afghanistan and Pakistan. Three remaining polio-endemic countries are Afghanistan, Nigeria and Pakistan [36,37].

The last country in East and Southern Africa to report paralytic polio caused by wild polioviruses was Ethiopia in 2014 from importation[38]. Tanzania started to implement Polio Eradication Initiative activities in 1995 based on the strategies and approach developed globally that had succeeded in achieving polio free status in other parts of the world. Like many other countries in the World, the focus was on polio eradication rather than permanent control including surveillance to immunization through Polio Vaccine Vaccination.

The introduction and implementation of any vaccine represent an additional expenses and costs which require allocation and adjustment of the health care system budget. Despite increased efforts and spending toward polio eradication, it has yet to be eliminated worldwide. Historically, Financial Resource Requirements from the Global Polio Eradication Initiative, as well as vaccination and population data from publicly available sources, establishes costs for routine immunization, immunization campaigns, surveillance and laboratory resources, technical assistance, social mobilization, treatment, and overhead.

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[33] National Documentation for the Certification of Poliomyelitis Eradication,October 2015

[34] World Health Organization. Global eradication of poliomyelitis by the year 2000, WHA41 28. WHO. May 1988:2-4. Google Scholar

[35] World Health Organisation. Polio endgame strategy 2019-2023: eradication, integration, certification and containment. WHO. 2019:19-46. Google Scholar

[36] World Health Organisation. Polio this week as of 26 May 2020. 2020. Accessed on 17 May 2020.

[37]Bahl S, Bhatnagar P, Roland WS, Roesel S, Zaffran M. Global polio eradication - way ahead. Indian J Pediatr. 2018;85(2):124- 131. PubMed | Google Scholar

[38] World Health Organisation. Polio this week as of 31 October 2018. 2018. Accessed on 31 October 2018.

i. Costs for Implementation of Poliovirus Vaccine

The injectable inactivated poliovirus vaccine (IPV) and the live, attenuated oral poliovirus vaccine (OPV)4 both provide full and likely permanent protection from polio, but differ in costs being higher for IPV and lower for OPV[39]. The differences in prices, depends on advantages and disadvantages of each vaccine formulation and administration[40,41]. Table 1, summarizes of costs acquisition for Gavi and Non Gavi countries to $0.15 and $0.20 respectively for the OPV and $2.05 and $3.51 respectively for the IPV. The cost of treatment for Polioviruses patient ranges from $700 for lower income countries to $750,000 to higher income countries as provided in Table 1.

[39] Sutter RW, Kew OM, Cochi SL, Aylward RB. Poliovirus vaccine – Live. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. Sixth ed. Philadelphia: Saunders Elsevier 2013:598–645.

[40] . Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, et al. Expert review on poliovirus immunity and transmission. Risk Anal. 2013;33(4):544–605.

[41] Hird TR, Grassly NC. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. PLoS Pathog. 2012; 8(4):e1002599.

Table 1 : Unit Costs Inputs

Cost Category	Setting	Cost
OPV dose cost per person	Gavi Country	$0.15
	Non Gavi Country	$0.20
IPV dose cost per person	Gavi Country	$2.05
	Non Gavi Country	$3.51
Routine delivery cost per person	DTP1 < 80% Coverage	$1.30
	DTP1 > 80% Coverage	$2.46
Treatment Cost per person with Polio AFP Case	Low income	$700
	Lower to middle income	$7000
	Upper Income	$70,000
	High income	$750,000

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ii. Costs for Implementation of Poliovirus Vaccine Based of Country's by World Bank Income Level (WBIL)

In order to obtain global economic analyses, we ignore differences in vaccine costs within a country. We stratify countries according to their World Bank Income Level (WBIL): High Income (HI), High to Upper (UMI), Lower Middle (LMI), and Low Income (LI) countries (World Bank, 2019)[42]. This approach is based on the fact that, countries face different poliovirus risks, which imply different benefits associated with continued and future use of oral poliovirus vaccine (OPV) and/or inactivated poliovirus vaccine (IPV). With the Global Polio Eradication Initiative (GPEI) continuing to extend its timeline for ending the transmission of all wild polioviruses and to introduce new poliovirus vaccines, the polio vaccine supply chain continues to expand in complexity [43]. The increased complexity leads to significant uncertainty about supply and costs.

[42] World Bank. (2019). World Bank list of economies (June 2019). Retrieved from http://databank.worldbank.org/data/download/site-content/CLASS.xls

[43]Kimberly M. Thompson and Dominika A. Kalkowska, 2021:, Potential Future Use, Costs, and Value of Poliovirus Vaccines. Risk Analysis Vol. 41, No. 2, 2021 DOI: 10.1111/risa.13557

Notably, the strategy of phased OPV cessation of all three serotypes to stop all future incidence of poliomyelitis depends on successfully stopping the transmission of all wild polioviruses. Countries also face challenges associated with responding to any outbreaks that occur after OPV cessation, because stopping transmission of such outbreaks requires reintroducing the use of the stopped OPV in most countries. National immunization program leaders are always likely to consider differences in their risks and willingness-to-pay for risk reduction as they evaluate their investments in current and future polio vaccination. Information about the costs and benefits of future poliovirus vaccines, and discussion of the complex situation that currently exists, should prove useful to national, regional, and global decision makers and support health economic modeling. Delays in achieving polio eradication combined with increasing costs of poliovirus vaccines continue to increase financial risks for the GPEI[Error! Bookmark not defined.]. The information provided in Table 2, summarized the costs of for acquisition, administration and application of poliovirus vaccines in different formulation through various approaches. Based on the provided in Table 2 below.

The costs of for acquisition of the Poliovirus Vaccine for a Lower Middle Income like country Tanzania in different formulation and application/introduction approaches are: OPV RI $ 0.19; OPV+IPV (3rd RI dose), full $ 3.50; OPV +IPV (3rd RI dose) fractional with needle $1.07; OPV+IPV (3rd RI dose), fractional with device $1.07; OPV+IPV (3rd RI dose), fractional with Vaccine Patch $1.95; nOPV RI $0.38; nOPV+IPV (3rd RI dose), full $3.69; nOPV +IPV (3rd RI dose) fractional with needle $1.26; nOPV+IPV (3rd RI dose), fractional with device $1.26; nOPV+IPV (3rd RI dose), fractional with Vaccine Patch $2.14; IPV RI Single Full $ 3.12; IPV RI Single fractional with needle; $0.76; IPV RI Single fractional with device $0.76; IPV RI Combo dose $5.00; IPV Vaccine Patch, RI or SIA $1.77; OPV in pSIA $0.18; OPV in oSIA $0.18; nOPV in pSIA $0.35; nOPV in oSIA $0.35; IPV SIA Single full $3.12; IPV SIA Single Fractional with needle $0.62 and IPV SIA Single Fractional with device $0.6243 (Table 2).

These costs analysis provides opportunity for the country to decide on the two vaccines considering the fact that, poliovirus vaccines is unlike many other vaccine-preventable diseases as it can occur with either or both of two vaccines with different benefits, risks, and costs: OPV and inactivated poliovirus vaccine

(IPV)[44]. The relatively cheap-to-produce and deliver live, attenuated OPV infects recipients who can secondarily infect and induce or boost immunity in others in the community. In addition, the information summarized in table 2 provides the best estimates of polio vaccine cost and valuation inputs for different income levels considering the information available on by January 1, 2020 and estimates for vaccine antigen price per dose in actual price lists provided by UNICEF, 2019 [45].

[44] Duintjer Tebbens, R. J., Pallansch, M. A., Chumakov, K. M., Halsey, N. A., Hovi, T., Minor, P. D., Thompson, K. M. (2013b). Review and assessment of poliovirus immunity and transmission: Synthesis of knowledge gaps and identification of research needs. Risk Analysis, 33(4), 606–646.

[45] UNICEF. (2019). UNICEF Supply and Logistics - Vaccine price data (IPV last updated 25 October 2018, OPV last updated 25 July 2019). Retrieved from https://www.unicef.org/supply/index_57476.html

Table 2 : Summary of Costs in 2019 US Dollars (US$2019) by Type of Immunization Contact by World Bank Income Level

Cost inputs by WBIL (US$2019)	Vaccine Costs Contact (w/wastage)				Administration Cost per Contact				Total Cost per Contact			
Contact Type	**LI**	**LMI**	**UMI**	**HI**	**LI**	**LMI**	**UMI**	**HI**	**LI**	**LMI**	**UMI**	**HI**
OPV RI	0.19	0.19	0.39	9.72*	0.95	0.95	2.51	3.18*	1.14	1.14	2.90	12.90*
OPV+IPV (3rd RI dose), full	3.31	3.50	5.98	NA	1.95	1.95	5.51	NA	5.26	5.45	11.49	NA
OPV +IPV (3rd RI dose) fractional with needle	1.02	1.07	1.57	NA	1.95	1.95	5.51	NA	2.97	3.02	7.09	NA
OPV+IPV (3rd RI dose), fractional with device	1.02	1.07	1.57	NA	2.25	2.25	5.81	NA	2.97	3.02	7.09	NA
OPV+IPV (3rd RI dose), fractional with device	1.92	1.95	3.37	NA	1.90	1.90	5.02	NA	3.82	3.85	8.39	NA
nOPV RI	0.38	0.38	0.77	9.72*	0.95	0.95	2.51	3.18*	1.32	1.32	3.29	12.90*
nOPV+IPV (3rd RI dose), full	3.50	3.69	6.36	NA	1.95	1.95	5.51	NA	5.45	5.64	11.87	NA
nOPV +IPV (3rd RI dose) fractional with needle	1.21	1.26	1.96	NA	1.95	1.95	5.51	NA	3.16	3.21	7.47	NA
nOPV+IPV (3rd RI dose), fractional with device	1.21	1.26	1.96	NA	1.95	1.95	5.81	NA	3.46	3.51	7.77	NA
nOPV+IPV (3rd RI dose), fractional with Vaccine Patch	2.11	2.14	3.75	NA	1.90	1.90	5.02	NA	4.00	4.04	8.78	NA
IPV RI Single Full	2.94	3.12	5.28	15.02	1.78	1.78	4.69	17.06	4.72	4.87	9.97	32.08
IPV RI Single fractional with needle	0.71	0.76	1.19	NA	1.78	1.78	4.49	NA	2.49	2.53	5.88	NA
IPV RI Single fractional with device	0.71	0.76	1.19	NA	2.08	2.08	4.99	NA	2.79	2.83	6.18	NA
IPV RI Combo dose	4.38	5.00	7.75	30.12	0.30	0.30	0.78	2.84	4.67	5.30	8.53	32.96

IPV Vaccine Patch, RI or SIA	1.73	1.77	2.98	27.38	0.95	0.95	2.51	3.18	2.68	2.71	5.49	30.56
OPV in pSIA	0.18	0.18	0.37	9.72*	O.95	0.95	2.51	3.18*	1.12	1.12	2.88	12.90*
OPV in oSIA	0.18	0.18	0.37	9.72*	0.95	0.95	2.51	3.18*	1.12	1.12	2.88	12.90*
nOPV in pSIA	0.35	0.35	0.73	9.72*	0.95	0.95	2.51	3.18*	1.30	1.30	3.24	12.90*
nOPV in oSIA	0.35	0.35	0.73	9.72*	0.95	0.95	2.51	3.18*	1.30	1.30	3.24	12.90*
IPV SIA Single full	2.94	3.12	5.28	15.86	1.78	1.78	4.69	17.06	4.72	4.89	9.97	32.91
IPV SIA Single Fractional with needle	0.59	0.62	1.06	NA	1.78	1.78	4.69	NA	2.36	2.40	5.75	NA
IPV SIA Single Fractional with Device	0.59	0.62	1.06	NA	2.08	2.08	4.69	NA	2.66	2.70	6.05	NA

HI = high income; IPV = inactivated poliovirus vaccine; LI = low income; LMI = lower middle income; NA = not applicable; nOPV = novel oral poliovirus vaccine; OPV = oral poliovirus vaccine; RI = routine immunization; SIA = supplemental immunization activity; UMI = upper middle-income; WBIL = World Bank Income Level.
Note: *Estimate for HI included for theoretical comparison.
Source: Kimberly M. Thompson and Dominika A. Kalkowska, 2021[43]

iii. Production Capacity and Available Supplies

The world has made incredible progress toward polio eradication, reducing polio cases by 99.9% in the last 30 years[46]. But the last steps in ending this disease are proving the most difficult, particularly with continuing outbreaks of circulating vaccine-derived polio viruses (cVDPVs)[46.] In 2020, the WHO listed the nOPV2 vaccine for emergency use (EUL) to address the rising cases of a vaccine-derived polio strain in a number of African and East Mediterranean countries through Bio Farma of Indonesia as a responsible manufacturing company of vaccine.

Additionally, in the collaboration with PATH and Bio Farma as one of the world's leading OPV manufacturers, Batavia Biosciences is also currently producing attenuated and safe novel oral polio vaccine (nOPV) candidates[47]. The nOPV2 vaccine to be developed and produced is under the grant from the Bill & Melinda Gates Foundation and it is the first nOPV vaccine to go through clinical development, to be followed by vaccines for nOPV1 and nOPV3[47]

The EUL pathway involves a rigorous assessment of phase II and phase III clinical trial data as well as substantial additional data on safety, efficacy and manufacturing quality. In addition, the decision of whether to use the vaccine, each country needs to complete a readiness process for the implementation of the vaccine under the EUL[46] .

As of 9 June 2021, 32 countries were undergoing the readiness verification process for nOPV2 use and, of these 32, 7 had been approved. Up to this date, 18,752,409 doses of nOPV2 had been administered, primarily in Nigeria (17,899,130 doses) and Liberia (853,279 doses), and 5 711,268 children were targeted for vaccination in Benin, Democratic Republic of the Congo, Sierra Leone and Tajikistan in the completed first round[48].

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[46]WHO's Emergency Use Listing Procedure of nOPV2, 2020. Development of a new safer Oral Polio Vaccine against type 2 strain (nOPV2) with lower risk of circulating vaccine derived polio virus (cVDVP) or vaccine associated paralytic poliomyelitis (VAPP) than existing Sabin mOPV 2 .

[47] Leiden, the Netherlands, Sep 16, 2019. Today, Batavia Biosciences announces it received a grant of $6.5 million from the Bill & Melinda Gates Foundation to develop a manufacturing process for a novel oral vaccine against polio virus type 2 strain (nOPV2) to help protect children worldwide from future polio outbreaks.

[48] Extract from GACVS meeting of 8-9 June 2021, published in the WHO Weekly Epidemiological Record of 23 July 2022

The company producing the vaccine is committed to continue generating data to enable full licensure. On the other hand, WHO prequalification will assess additional clinical data generated from vaccine trials and deployment on a rolling basis to ensure the vaccine continues to meet the necessary standards of quality, safety and efficacy for broader availability through procurement by UN agencies and others.[47]

iv. Vaccine Affordability

The financing for introduction and implementation of the *nOPV2* follows the procedure of Global Polio Eradication Initiative (GPEI) which recommends uses of four-pronged polio eradication strategy standard namely routine immunization, supplementary immunization activities, mop-up campaigns in high-risk districts, and surveillance[49]. The polio program has a similar architecture in countries of outbreak, even as operational realities vary. In both countries the program is integrated into the expanded program on immunization (EPI) at the operational level and service delivery follows the three-tiered structure of the health system, from peripheral to central levels including primary, secondary, and tertiary or specialized care.

The funding and technical assistance of the program in countries with poliovirus outbreak is provided by GPEI partners [50]. The total costs for acquisition and administration of *nOPV2* during outbreak in Lower Middle Income countries like including Tanzania, using different formulation and application/introduction approaches is estimated to be *nOPV* in *oSIA* $1.30[43]

v.Economic and Social Impact

In the fight to eradicate poliovirus many strategies have been implemented worldwide. Strategies such as supplemental immunization activities (SIAs) using oral poliovirus vaccine (OPV), reported to increase immunization coverage beyond the levels achieved by national age-schedule-based routine immunization (RI). The approach includes large, planned and preventive campaigns (pSIAs) that reach large numbers of children within a specific age range independent of prior immunization, but SIAs can also include reactive, outbreak response campaigns (oSIAs).

[49] Deressa, W., Kayembe, P., Neel, A.H. et al. Lessons learned from the polio eradication initiative in the Democratic Republic of Congo and Ethiopia: analysis of implementation barriers and strategies. BMC Public Health **20,** 1807 (2020). https://doi.org/10.1186/s12889-020-09879-9

[50] Ethiopia CCG. Contributing towards polio eradication in Ethiopia: AFP case detection and status of surveillance in pastoralist and semi-pastoralist communities of CORE Group Polio Project implementation districts (wordeas) in Ethiopia. Addis Ababa: CCRDA/CORE Group Ethiopia; 2012. https://coregroup.org/wpcontent/uploads/2017/08/Newborn_Tracking_of_ OPV0_Final_FOR_PRINTING-1.pdf.

Therefore eradication of polioviruses depending on permanent prevention of transmission, is not recommended as it represents a failure with respect to achieving the ultimate goal.[51] Furthermore it is recommended that prior to OPV2 cessation, Global Polio eradication initiative (GPEI) and countries should recognize the existing immunity gap for serotype 2 as it has impact on immunization with tOPV prior to OPV2 cessation so as to prevent cVDPV2s before and after OPV2 cessation[52].

vi.Economic Impact on the Immunization Programme

Based on the literatures reviewed nOPV2 is the best option if its properties are ideal (no reversion, no VAPP), but that stopping outbreak response to wait for nOPV2 for a period of 6 months may increase the expected cVDPV2 cases by more than 1,000 in the African region by end of 2023 compared to continuing to use mOPV2 promptly for oSIAs. In addition, uncertainty remains as to whether nOPV2 will exhibit properties more like those characterized by the model as ideal or not ideal. Overall, any delay in outbreak response increases the expected number of cVDPV2 cases, the risk of spread of cVDPV2 to additional subpopulations, the scale of outbreak response required, and the probability of needing to restart OPV2 broadly in preventive immunization [53].

- **Reduction in health care costs**

Based on the literature, there are less information on impact of the vaccine in reduction of health care cost. Many studies focus on the impact of the vaccine in fighting against vaccines derived virus outbreak and its efficacy comparing to the existing vaccines with similar characterization.

- **Health gains (years of life saved, QALY gained, etc.) and cost effective ratio**

The Global Polio Eradication Initiative (GPEI) agreed to introduce a genetically stabilized, novel OPV type 2 (nOPV2) that has a lower risk for generating VDPV2 than does Sabin mOPV2; if nOPV2 is successful in limiting new VDPV2 emergences, GPEI foresees the replacement of Sabin mOPV2 with nOPV2 for cVDPV2 outbreak responses during 2021 with the comment that the vaccine substantially lower risk for reversion to neu-rovirulence [54] .

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[51] Kimberly M. Thompson and Dominika A. Kalkowska, 2020. Reflections on Modeling Poliovirus Transmission and the Polio Eradication Endgame. DOI: 10.1111/risa.13484

[52] Dominika A. Kalkowska et al 2020. Updated Characterization of Outbreak Response Strategies for 2019–2029: Impacts of Using a Novel Type 2 Oral Poliovirus Vaccine Strain. DOI: 10.1111/risa.13622

[53] Dominika A. Kalkowska et al 2021. Serotype 2 oral poliovirus vaccine (OPV2) choices and the consequences of delaying outbreak response. https://doi.org/10.1016/j.vaccine.2021.04.061

[54] Mary M. Alleman et al, 2020. Update on Vaccine-Derived Poliovirus Outbreaks — Worldwide,July 2019–February 2020. www.ncbi.nlm.nih.gov/pmc/articles/PMC7188410/pdf/mm6916a1.pdf

D. Health Policy and programmatic issues

i. Interaction with other existing interventions& control strategies

Impact of programme on safety & efficacy of other vaccines & other health care sectors

National immunization programs continue to rely on both Sabin-strain oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). The countries supported by the Global Polio Eradication Initiative (GPEI) currently include OPV in their routine immunization (RI) schedules by delivering 3 doses of bivalent OPV (bOPV, containing OPV serotypes 1 and 3) and one dose of IPV (containing serotypes 1, 2, and 3) given with the third bOPV dose. The polio end game strategy includes ending the use of all OPV after the certification of wild poliovirus (WPV) eradication[55], which the GPEI decided to implement in phases by serotype. The GPEI globally coordinated the cessation of type 2-containing OPV (OPV2) in May 2016[56], which stopped all use of trivalent OPV (tOPV, containing all three OPV serotypes) in RI and replaced it with bOPV in OPV-using countries. Many GPEI-supported countries also perform periodic supplementary immunization activities (SIAs). The SIAs may include preventive SIAs (pSIAs) using bOPV to increase population immunity for serotypes 1 and 3 or outbreak response SIAs (oSIAs) that use bOPV or a serotype 2 monovalent OPV (mOPV2). As of late 2020, some countries may also potentially use trivalent OPV (tOPV) for some oSIAs based on current GPEI plans.

The use of nOPV2 while under EUL will require verification that a country has met a series of readiness requirements, from securing national approvals for demonstrating adequate preparation across vaccine management, surveillance, safety, training, communications and laboratory. The verification of readiness must be issued prior to the release of nOPV2 to a given country from the global stockpile/reserve supply [57].

[55] World Health Organization Global Polio Eradication Initiative. Polio eradication and endgame Strategic Plan (2013-2018). http://polioeradication. org/wp-content/uploads/2016/07/PEESP_EN_A4.pdf; 2013 [accessed Jun 4,2019].
[56] Hampton LM, Farrell M, Ramirez-Gonzalez A, Menning L, Shendale S, Lewis I, et al. Cessation of trivalent oral poliovirus vaccine and introduction of inactivated poliovirus vaccine - Worldwide, 2016. MMWR 2016;65:934–8.

[57] 5 https://www.who.int/news-room/events/detail/2020/10/05/default-calendar/sage_meeting_october_2020

According to the New Vaccine Deployment Plan developed by IVD (2021), the introduction of new vaccine needs sector wide approach interrelation and collaboration. The sectors involvements consider the areas of planning and coordination, service delivery, demand delivery and evaluation, and surveillances. This should go beyond ministry of health and its sectors/departments through involving the policymakers, religious leaders, private and public health facilities, different immunisation partners (WHO, UNICEF, CDC, USAID) and other community influential people[58].

Disruption of others interventions

Some recent studies explore the impacts of disruptions associated with the COVID-19 pandemic on other maternal and child health interventions[59] and the management of vaccine-preventable diseases[60]. However, to date, no studies report on the likely global impacts of COVID-19 on polio eradication objectives. This analysis seeks to characterize the uncertain impacts on immunization activities and poliovirus transmission using assumptions consistent with information available as of Januray 18, 2021.

ii. Feasibility

- **The trends in routine EPI vaccine coverage in the country**

Tanzania Immunisation Program was established in the 1970s. It started with three vaccines which targeted three diseases namely Smallpox, Tuberculosis and Pertussis. It continues to expand its services by adding more vaccine as per resources availability and scientific evidences. Currently the program is having a total of routine nine vaccines types which prevents thirteen diseases. However, from the year 2021, the program started implementing COVID 19 vaccination campaign program. These vaccines are available and being delivered by all health facilities registered by the program, which is 6784 both public and private facilities. Tanzania immunization services aimed to achieve and sustain the vaccination coverage of >90% nationally and >80% at every district in line with Global

[58] https://www.afro.who.int/news/risks-and-challenges-africas-covid-19-vaccine-rollout, accessed Sept 16, 2021.

[59] Roberton T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. Lancet Global Health 2020;8(7):e901–8.

[60] Abbas K, Procter SR, van Zandvoort K, Clark A, Funk S, Mengistu T, et al. Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit–risk analysis of health benefits versus excess risk of SARSCoV- 2 infection. Lancet Glob Health 2020, 8,(10):e1264 - e1272.

Vaccine 4 Action Plan (GVAP 2010 - 2020). Despite several challenges, the IVD program has achieved and sustained the coverage of DTP3, OPV3, PCV3, Rota2, and MCV1 above 90% at the national level for a period of 2016 to 2020, with exception of OPV3 in 2020 which dropped to 74%[61]. The performance of Acute Flaccid Paralysis(AFP) surveillance has been varying among different years but maintained above 2 for the period between 2012 -2014 (Figure 3 & 4).

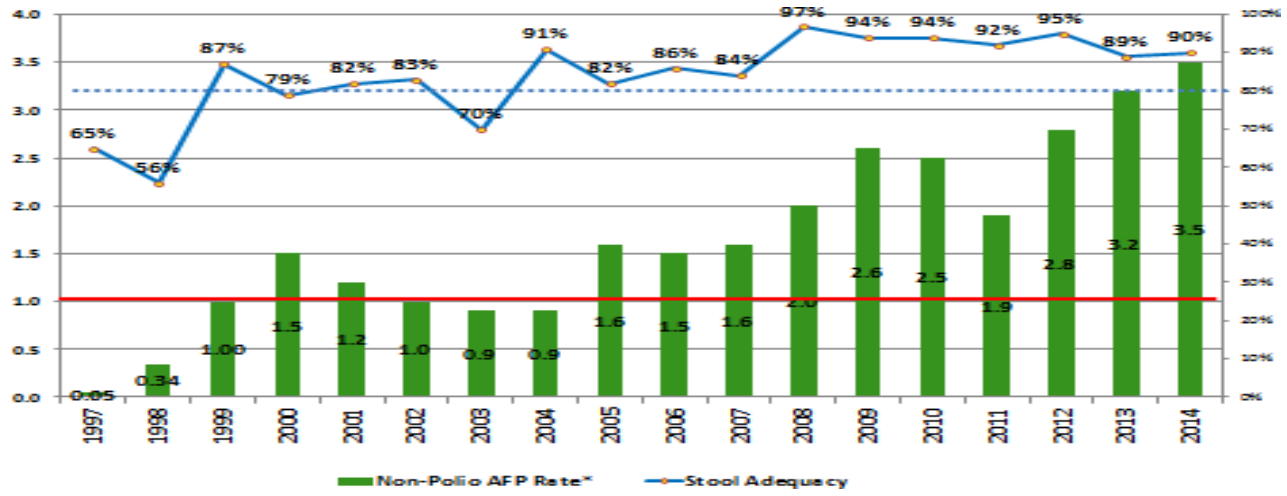

Figure 3 : Summary of Non -Polio AFP surveillance performance (National), Year 1997-2014

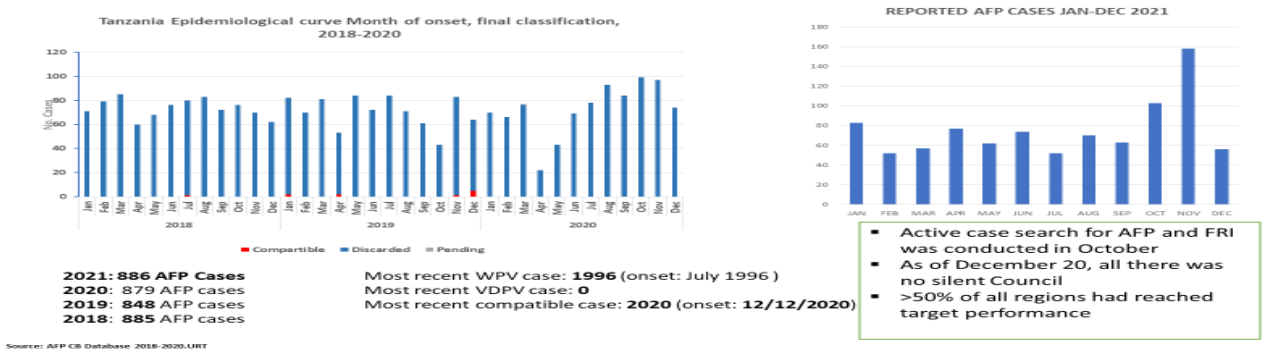

Figure 4 : *Trend of reported AFP cases 2018-2021*

iii. Vaccine registration

[61] *https://immunizationdata.who.int/listing.html?topic=&location=*

In 2019 and 2020, the Bill & Melinda Gates Foundation (BMGF) worked closely with multiple product development partners to support P.T. Bio Farma's, **Indonesian** submission to the WHO Emegernce Use Listing Procedure (EUL) for the novel oral polio vaccine type 2 (nOPV2) vaccine. The novel OPV2 vaccine (nOPV2) has been developed and designed to be less likely to mutate into a form that can cause cVDPVs and vaccine-associated paralytic polio (VAPP) [62].

The novel vaccine became the first vaccine to be submitted and approved by WHO Emergence Use Listing (EUL) under the revised procedure. Novel Oral Poliomyelitis Vaccine type 2 (nOPV2) has been granted time limited use under Emergency Use Listing procedure by WHO, on 13 November 2020. This decision was subject to commitments by the manufacturer the following [62]

a) Continue development of the product towards prequalification, according to the EUL procedure;
b) Additional quality data in accordance with the quality assessment report;
c) Full implementation of the RMP which includes the monitoring of the safety, effectiveness and programmatic aspects
d) Conduct Lot to lot consistency study;
e) Provide reports of quality complaints from the field for batches supplied;
f) Provide notification of any problems/constraints in production or quality control which might affect the inclusion into the stockpile for emergency use.

The TMDA has in palce the the Guidelines to be followed for the application of product which does qualify for normal registration procedure.In view of this, the approval procedure will use the Guidance on Processing Applications for registration of Medicinal Products through non-routine procedure in Tanzania, 1st Revision, March, 2020[63]. TMDA will have to handle and finalize internal administrative procedure to make sure the vaccine is made available in the Country for public use in case of outbreak

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iv) Impact on resources

[62] The World Health Organization. WHO statement on the meeting of the International Health Regulations Emergency Committee concerning the international spread of wild poliovirus. https://www.who.int/mediacentre/news/statements/ 2014/polio-20140505/en/ (2020).

[63] Made under Regulation 4 (1) of the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015

The the novel oral polio vaccine type 2 (nOPV2) vaccine is ready to use vaccine packed in a vial of 50 doses, there is a need to adhere to WHO Multi-dose Vial Policy Statement of WHO[64]. The implementation of the nOPV2) vaccine will require costs related to: -

i) Development of a training plan and training of health care staff across all health facilities on protocols to administer nOPV2).
ii) Establishment/strengthening of the national logistics and standard operating procedures to coordinate deployment of the vaccine,
iii) Strengthening of distribution strategies in relation to existing cold chain as result of additional load in the system,
iv) Mapping and development of a plan to provide for infrastructure needs,
v) Developing and distributing appropriate standard operating procedures (SOPs), protocols, or guidelines and IEC materials.
vi) Sensitization of all stakeholders at national, sub-national and community levels.

The implementation of nOPV2 will require the IVD programme to consider all of the issues above for a smoother implementation. The programme can map out what has been achieved during oPV1 and IPV vaccine introduction and what is required specifically for introduction of the nOPV2 in case of the outbreak.

v) Ability to evaluate

- **Availability of information systems to manage the vaccine supply chain & measure related performance metrics i.e. coverage& vaccine utilization**

Immunization and Vaccine (IVD) Development Program formely known as Expanded Programme on Immunization is under the Directorate of the Preventive Service of the Ministries of Health for both Tanzania Mainland and Zanzibar. The Programme Manager oversees and supervises the functions of the Programme. The Programme comprises seven main sections; administration, operations, surveillance, monitoring and evaluation, cold chain and logistics, social mobilization, and training. Other functions include monitoring, training, technical support, supervision, procurement and

[64] *World Health Organization.* WHO policy statement: multi-dose vial policy (MDVP): handling of multi-dose vaccine vials after opening. *No. WHO/IVB/14.07. World Health Organization, 2014.*

distribution of vaccines, equipment and related supplies and ensuring adherence to quality service delivery.The IVD Program has the Surveillance Unit which works closely with Epidemiology and Disease Control section it has the mandate to oversee the Integrated Disease Surveillance and Response in the country. In addition, there is the Cold chain and Logistics unit work closely with National Regulatory Authority on the vaccine management.

Collaboration exists between IVD Program Tanzania Mainland and Zanzibar on the Polio Eradication Initiative (PEI). Due to same PEI strategies, the two programs work together in development, implementation, monitoring and evaluation through the designated polio committees appointed by both ministries. In addition, the two programmes use the same AFP and Measles surveillance data base. Currently, there is a system to conduct AFP surveillance activities throughout the country and is structured as Figure V. In addition, three committees (National Certification Committee (NCC), National Polio Expert Committee (NPEC), National Task Force (NTF) for Laboratory Containment of Poliovirus) exist and are functioning well.

AFP Surveillance – Organization chart

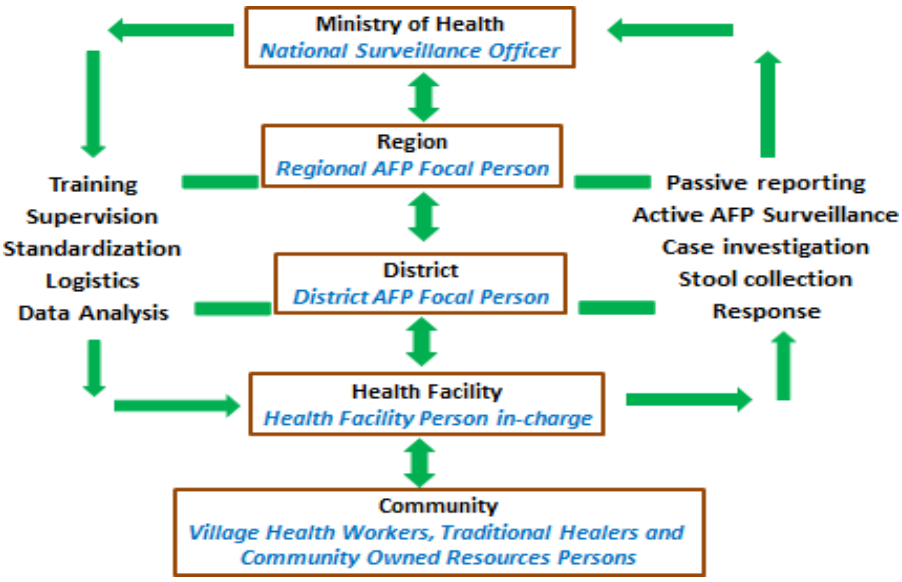

Figure V:

Figure 5 : Organizational chart for surveillance activities in Tanzania

All health facilities in Tanzania are designated as AFP active surveillance sites. Hospitals and Health Centers are categorized as high and medium priority sites respectively depending on the possibility of the AFP case visiting the facilities. Clinicians have received train to detect, notify, investigate and report all AFP cases. The system has weekly, monthly, and quarterly reporting forms. However, the AFP surveillance is not limited to health facilities; it extends to involve community sites with potential of caring for AFP cases such as traditional healers/ herbal clinics or those with proximity to the community including community health care workers, influential community, and spiritual leaders in some communities.

Implementation of nOPV2 will require the environmental surveillance, the country established Environmental Surveillance (ES) for Polio in April 2019. A total of fifteen sites were identified and visited to assess the eligibility of the sites in accordance with criteria. Four sites with closed drainage systems were established in three Councils of Dar es salaam region: Buguruni and Kipata sites in Ilala Councils, Mabibo site in Ubungo Council and Msasani site in Kinondoni Council. Since establishment in 2019, all sites have been performing well above average and sample packed and transported under reverse cold chain to Uganda Virus Research Institute (UVRI) for testing. All the four sites have attained the target indicator for isolation of EV >50% [65].

vi) Acceptability

- **Perception of the public & medical community about the disease & the vaccine**

Vaccine perceptions among acceptors and non-acceptors of childhood vaccination on oral polio vaccine were explored in Nigeria, that is to say, acceptors and non-acceptors among mothers of children under five years were interviewed in-depth with an interview guide that assessed vaccine acceptance, social and personality factors, and health belief model (HBM) categories in relation to oral polio vaccine (perceived susceptibility, severity, cost barriers, general barriers, benefits, knowledge, and engagement in preventative health behaviours). Community leaders were purposively selected while parents were selected based on availability while ensuring the different attitude to vaccines was covered. Results showed that the HBM framework was found to be appropriate for identifying and distinguishing vaccine acceptors and non-acceptors. In addition, the HBM categories of benefits and susceptibility were found to influence oral polio vaccine acceptance. Second, the opinion of family members about the oral polio vaccine moderated the relationship between number of social ties and vaccine acceptance. Further, oral polio vaccine acceptance was related to outbreaks of paralysis of any sort, but not aggregate scores of other preventative health behaviours. Implications of this study include the investigation of vaccine acceptance in a high-risk population[66].

Polio risk perception was low among study participants. The majority (59%) of caregivers' participants, believed that vaccination was either not necessary or would not be helpful, and 30% thought it might be harmful. Religious beliefs were an important driver in the way people understood

[65] https://www.afro.who.int/news/searching-polio-unusual-places-tanzania

[66] Murele B, Vaz R, Gasasira A, Mkanda P, Erbeto T, Okeibunor J. Vaccine perception among acceptors and non-acceptors in Sokoto State, Nigeria. Vaccine. 2014 May 30;32(26):3323-7. doi: 10.1016/j.vaccine.2014.03.050. Epub 2014 Apr 5. PMID: 24713368.

disease. Fifty-two percent of 48 respondents reported that illnesses were due to God's will and/or destiny and that only God could protect them against illnesses. Only a minority (14%) of respondents indicated that polio was a significant problem in their community [67].

The significant result in Nigeria that was made has relationship to our Nation, mOPV2 was widely applied to the children in Tanzania and was perceived positively with coverage above 74% between 2016 and 2020(Figure 6)

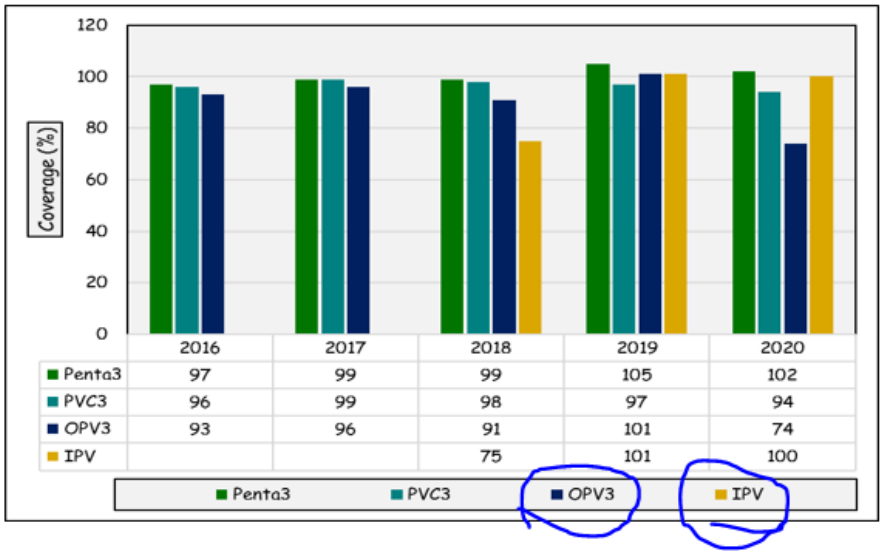

Figure 6 : Trend of immunization coverages for vaccine antigens given at the same schedule (2016-2020)

For the nOPV2 emergence use of polio vaccination shall be applied on campaign mode.For the fore coming polio emergence use of vaccine, nOPV2, according to the scientific study is more effective and modified therefore high acceptance is anticipated in Tanzania mainland.

vii) Social considerations

With reference to WHO Acute Flaccid Paralysis Surveillance Field Guide, of January, 2006 (AFP)[68] the mother of the children under five years old need to be educated on the significant and positive use of oral polio vaccination. In addition, the data from Tanzania showed that OPV vaccination was associated with rare cases of Vaccine Associated Paralytic Polio (VAPP) in vaccinated individuals or their contacts, or the emergence of vaccine-derived polioviruses (c)VDPV). Although nOPV2 is reported to have lower neurovirulence, it is unclear whether this translates into no or lower risk of VAPP or other non-paralytic polio associated neurotropic events[69] (e.g. aseptic meningitis, encephalitis). Possibly the same trend shall apply to nOPV2, being genetically modified, still needs to

[67] Michael CA, Ogbuanu IU, Storms AD, Ohuabunwo CJ, Corkum M, Ashenafi S, Achari P, Biya O, Nguku P, Mahoney F; NSTOP OPV Refusal Study Team. An assessment of the reasons for oral poliovirus vaccine refusals in northern Nigeria. J Infect Dis. 2014 Nov 1;210 Suppl 1:S125-30. doi: 10.1093/infdis/jiu436. PMID: 25316826.
[68] AFRO - AFP Surveillance Field Guide – January 2006
[69] https://pdfs.semanticscholar.org/b6f1/952ec14675ba975c72a255535b53faef4791.pdf?_ga=2.22986168.201269

be established, all requirement shall be used to administer the nOPV2 both, at the sites and centres of vaccination .
Notably, countries responded to COVID-19 by reducing or shutting down economic and social activities, which led to substantially decreased population mixing and health services, including reduced polio immunization [70].

viii) Equity

The use of emergence polio vaccine on nOPV2 is highly needed for effective prevention. A post-training survey demonstrated that, on average, 90% of health workers showed good knowledge of both new vaccines and of vaccine preventable diseases. In addition, EPI staff observed significant savings in the development of communications messages, materials, advertising, and in conducting social mobilization activities. These savings were highlighted in both vaccines because they targeted the same age group – infants. The group of infants is well stipulated in the ministry of Health (MoH) (IVD department) polio overview plan [71]

IV. Discussion

The world has made incredible progress toward polio eradication, reducing polio cases by 99.9% in the last 30 years [72]. But the last steps to ending this disease are proving the most difficult, particularly with continuing outbreaks of circulating vaccine-derived polio viruses (cVDPVs)[73].

The novel OPV2 vaccine was granted a WHO Emergency Use Listing (EUL) ON 13th November 2020 for use in response to circulating vaccine derived Polio virus type 2 (cVDPV2). Early clinical trials have demonstrated that nOPV2 has similar immunogenicity to monovalent OPV2. However, five genetic modifications on the genome of nOPV2 polio vaccine candidate carries increased genetic stability, hence slowing Sabin2 virus evolution preventing reversion to virulence while preserving the

[70] World Health Organization Global Polio Eradication Initiative. Call to action to support COVID-19 response. https://polioeradication.org/news-post/call-toaction- to-support-covid-19-response/; 2020 [accessed August 20, 2020].

[71] https://www.who.int/immunization/diseases/...

[72] *WHO's Emergency Use Listing Procedure of nOPV2, 2020. Development of a new safer Oral Polio Vaccine against type 2 strain (nOPV2) with lower risk of circulating vaccine derived polio virus (cVDVP) or vaccine associated paralytic poliomyelitis (VAPP) than existing Sabin mOPV 2 .*

[73] *Kimberly M. Thompson and Dominika A. Kalkowska, 2021:, Potential Future Use, Costs, and Value of Poliovirus Vaccines. Risk Analysis Vol. 41, No. 2, 2021 DOI: 10.1111/risa.13557*

antigenic and immunogenic characteristics, overall replication strength and thermo-sensitivity characteristics.

Safety data from clinical trials, and surveillance from six countries where a nOPV2 has been deployed, have demonstrated a favorable safety profile compared to other oral polio vaccines used in routine childhood vaccination. Surveillance data from Nigeria showed that, out of 88,140,212 doses administered, the reporting frequency of VAPP was 0.007/100,000 vaccines which is far less compared to 0.025-0.4/100,000 vaccines in mOPV2. However, effective continuous surveillance is important to fully characterize the safety, efficacy, and effectiveness of the candidate vaccine. Furthermore , there is a need of sustained environmental surveillance for circulating vaccine derived poliovirus.

The TITAG noted that, the novel Oral Poliomyelitis Vaccine type 2 (nOPV2) has been granted time limited use under Emergency Use Listing procedure by WHO, on 13 November 2020. TMDA will have to handle and finalize internal administrative procedure to make sure the vaccine is made available in the Country for public use in case of outbreak. In addtion, it was noted that, the candidate vaccine should be stored at -20°C but it remains viable for up to three months when stored between+2 °C and +8 °C. Therefore, the cold chain logistics in place and storing capacity in Tanzania can accommodate the storage, distribution, and administration of the candidate vaccine in case of vaccine derived poliovirus outbreak.

Currently, the financing and technical assistance for introduction and implementation of the *nOPV2* for countries with poliovirus outbreak is provided by Global Polio Eradication Initiative (GPEI) and its partners[46.] The total costs for acquisition and administration of *nOPV* during outbreak in Lower Middle Income countries including Tanzania, using different formulation and application/introduction approaches is estimated to be *nOPV* in *oSIA* $1.30. Although the Government is expected to incur about 13% of purchase cost to cover additional costs related to port clearance and other administrative costs.

The good coverage of OPV3 based on IVD data demonstrates that our community generally has a high acceptance of OPV3 which shows the likelihood of also accepting the nOPV2. However, it's important to ensure strong community mobilization using influential leaders in raising community awareness and thus update of nOPV2 in case of an outbreak in the country.

V. Recommendation (Appendix III)

Based on the available data, the desirable effects of using nOPV2 during Polio oubtreak outweighs the undesirable effects. Therefore, the TITAG **recommends** the use of nOPV2 vaccine in Tanzania in the target population during Circulating Vaccine Derived Poliovirus outbreak. However, active Adverse Events Following Immunization (AEFI) surveillance should be conducted during vaccine use in order to identify Adverse Events of Special Interest (AESI).

VI. ANNEXES

- **Appendix I: Policy research question**
- **Appendix II: Evidence search and evaluation: process and results**
- **Appendix III: Recommendation framework and specific queries**

Appendix I: Policy question

Policy question:	Should the nOPV2 be recommended during the Circulating Vaccine Derived Poliovirus outbreak?
Population	Target population
Intervention	nOPV 2 0.1ml given once during campaign
Comparison	No Polio vaccine
Outcomes	Symptomatic Polio cases Hospitalization due to Polio disease All-cause death

Appendix II: Summary of Safety Studies on nOPV2 Vaccine

Study	Scope	Adverse Events	Reference	Comments (Limitation)	Quality of evidence
The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study	Double blinded single center phase I trial among the Age group- 18-50 years with the aim of evaluating safety and immunogenicity of nOPV2 , presence and extent of viral shedding and the neurovirulence of the shed virus for 28 days.	No serious adverse event occurred during the study. Severe evens were reported in 6(40%) in vaccine candidate 1 and 8 participants (60%) in candidate 2. Most of these events were increased blood creatinine phosphokinase but were not accompanied by clinical signs Other events were increased aspartate aminotransferase, headache and diarrhea. Most of events resolved spontaneously.	Van Damme, P., De Coster, I., Bandyopadhyay, A. S., Revets, H., Withanage, K., De Smedt, P., ... & Gast, C. (2019). The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. *The Lancet*, *394*(10193), 148-158.	Single center study to minimize the risk of environmental release.	Moderate

Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials	Results are from two randomized trials controlled studies to evaluate safety and immunogenicity of novel OPV2 vaccines and monovalent OPVC2 vaccine among healthy adults aged 18-50 years of age.	All vaccines appeared safe; no definitely vaccine-related withdrawals or serious adverse events were reported. After first doses in previously OPV-vaccinated participants, 62 (62%) of 100 monovalent OPV2 recipients, 71 (71%) of 100 recipients of novel OPV2-c1, and 74 (74%) of 100 recipients of novel OPV2-c2 reported solicited systemic adverse events, four (monovalent OPV2), three (novel OPV2-c1), and two (novel OPV2-c2) of which were considered severe. Most frequent adverse events were headache, fatigue, abdominal pain, diarrhoea, and myalgia, with no difference in frequency or severity across groups. the original suspicion that this was due to excessive exercise by the affected participants living in containment appears to be confirmed, as grade 3 or 4 increases were rare and no consistent changes were observed in this larger novel OPV2 study	De Coster I, Leroux-Roels I, Bandyopadhyay AS, Gast C, Withanage K, Steenackers K, De Smedt P, Aerssens A, Leroux-Roels G, Oberste MS, Konopka-Anstadt JL. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials. The Lancet. 2021 Jan 2;397(10268):39-50.	None	High

Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials	A two single-centre, multi-site, partly-masked, phase II randomized trials was conducted in healthy cohorts of children (aged 1–4 years) and infants (aged 18–22 weeks) in Panama aimed to assess safety and immunogenicity of the two novel OPV candidates compared with a monovalent Sabin OPV in children and infant. A total of 684 participants were enrolled.	Vaccinations were safe and well tolerated with no causally associated serious adverse events or important medical events in any group. Solicited and unsolicited adverse events were overwhelmingly mild or moderate irrespective of vaccine or dose. Three participants developed SAEs with subsequent admission (pneumonia in monovalent OPV2, mild bronchitis 13 days after a second-high dose of novel OPV2-c1, and a soft tissue preauricular abscess 24 days after receiving high-dose novel OPV2-c2). None was causally associated with the vaccines. Most solicited adverse events, mainly consisting of transient loss of appetite, abnormal crying, irritability, and fever, and diarrhea were described as mild with few individuals having adverse events described as severe.	Sáez-Llorens X, Bandyopadhyay AS, Gast C, De Leon T, DeAntonio R, Jimeno J, Caballero MI, Aguirre G, Oberste MS, Weldon WC, Konopka-Anstadt JL. Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials. The Lancet. 2021 Jan 2;397(10268):27-38.	None	High (RCT)

		Only one solicited adverse event was considered to be causally associated with monovalent OPV2, whereas 15 solicited adverse events after novel OPV2-c1 and eight solicited adverse events after novel OPV2-c2 were considered causally associated.			

VII. Appendix III: Recommedation Framework

Criteria	Work Group Judgements	Evidence	Additional information
Problem			
Is the problem of public health importance?	**YES**	According to the Centers for Disease Control and Prevention (CDC) [74].Poliomyelitis is a crippling and potentially fatal infectious disease, caused by poliovirus which spreads from person to person and can invade an infected person's brain and spinal cord, causing paralysis (can't move parts of the body). This infectious viral disease mainly affects young children. It is transmitted through contaminated food and water, multiplies in the intestine, from where it can invade the nervous system[75].The WHO Executive Board has declared polio eradication a programmatic emergency for global public health. The world has the tools to improve quality, to reach and immunize children	None

[74] https://www.cdc.gov/globalhealth/immunization/default.htm accessed on 27thFebruary 2022

[75] https://www.who.int/health-topics/poliomyelitis accessed on 27th February 2022

Criteria	Work Group Judgements	Evidence	Additional information
		and eradicate polio. Despite the efforts to eradicate polio the disease rests endemic in a coule of developing countries that warranty the possibility of reemerging in countires certifeid polio free.	
Benefits and Harms			
How substantial are the desirable anticipated effects?	**MODERATE**	The available evidence suggests that nOPV2 (the first new OPV vaccines in over 50 years) could be associated with less paralytic (polio) disease and potentially a lower risk of leading to new outbreaks including reversion to viral virulence. This has been reported to be due to the superior genetic and phenotypic stability of nOPV2 strains compared to Sabin-2 strains that were subsequently shed from children aged 1 to 5 years [76,23].	Additional data from larger RCT and real life studies are needed to establish nOPV2 efficacy and effectiveness.

[76] Wahid et al Evaluating stability of attenuated Sabin and two novel type 2 oral poliovirus vaccines in children. npj Vaccines (2022)7:19 ; https://doi.org/10.1038/s41541-022-00437

Criteria	Work Group Judgements	Evidence	Additional information
How substantial are the undesirable anticipated effects?	**MINIMAL**	Novel OPV2 has demonstrated a comparable safety profile and immunogenity to other oral polio vaccines in phase I and II clinical trials in infants, children and adults which warranted a WHO emergency use listing. Data from 111,989,393 million doses of nOPV2 administered in Benin, Congo, Liberia, and Nigeria , Congo Brazzavile and Tajakistan with safety surveillance for AFP, SAFIs, AESIs, and environmental surveillance have not identified any significant safety concerns. For the 88,140,212 doses administered in Nigeria, 3 reports of suspected VAPP have been identified so far through surveillance in Nigeria, and judged by the National Experts Causality committees (NEC) as being consistent with a causal association, the reporting rate of 0.007/100,000 vaccines in Nigeria is below the expected range of VAPP associated with mOPV2 vaccine of 0.025-0.4/100,000 vaccines, and therefore would not indicate an unexpected safety concern.	Continuous surveillance of safety data from RCTs and more information from wider use from countries implementing the nOPV 2 use.

Criteria	Work Group Judgements	Evidence	Additional information
		The other 3 AEFI/AESI reports judged by the Nigeria national causality committees to be consistent with a causal association (anaphylaxis, allergic reaction and meningo-encephalitis) do not generate any new safety signals. The national causality committees in Congo, Benin, Liberia and Tajikistan have found no AEFI/AESI cases to be consistent with a causal association with nOPV2[77].	
Do the desirable effects outweigh the undesirable effects?	**Favour intervention**	Refer above details	Refer to above details
What is the overall certainty of this evidence for the critical outcomes? ***Effectiveness of the intervention*** ***Safety of the intervention***	 **MODERATE** **High**	Overall, nOPV2 provides comparable protection against poliovirus type 2 while being more genetically stable less likely to be associated with the emergence of type 2 circulating vaccine-derived poliovirus with a potential to sustainably stop outbreaks compared to the existing OPV2 vaccine[78].	See above

[77] nOPV2 vaccine safety-end of EUL initial use period report, 13 March 2021-24November 2021

[78] Polio Global Eradication Initiative https://polioeradication.org/nopv2/ accessed on 23 Feb 2022

Criteria	Work Group Judgements	Evidence	Additional information
		Safety studies from phase I and II studies, and ongoing vaccination campaigns in countries with vaccine induced poliovirus have not identified significant safety issues compared to other oral polio vaccines.	
Values			
Does the target population feel that the desirable effects are large relative to undesirable effects?	**PROBABLY YES**	The good coverage of bOPV third dose based on IVD data demonstrates that our community generally has a high acceptance of bOPV third dose which shows the likelihood of also accepting the nOPV2.	It's important to ensure strong community mobilization using influential leaders in raising community awareness and thus update of nOPV2 in case of an outbreak in the country. Data from continuous AFP surveillance for monitoring.
Is there important uncertainty about or variability in how much people value the main outcome?	**NO**	Polio vaccine has been used in routine immunization program since 1975 with high uptake. Furthermore the community is aware of the debilitating complications that result from polio infection. Thus, uncertainty is not likely.	Continue advocacy to maintain the current high vaccine uptake.
Acceptability			

Criteria	Work Group Judgements	Evidence	Additional information
Is the intervention acceptable to key stakeholders?	**YES**	Polio vaccines have been used in TZ since 1975 with good coverage,the same uptake is expected with implementation of nOPV2	However, implementation of nOPV2 during outbreak will be preceeded with risk coomunication and community engagement
Resource Use			
Is the intervention a reasonable and efficient allocation of resources?	**PROBABLY YES**	The financing and technical assistance for introduction and implementation of the nOPV2 for countries with poliovirus outbreak is provided mostly by Global Polio Eradication Initiative (GPEI) and its partners [79]. .However there is additional cost of about 13% of purchase cost that might be incurred by the government in relation to clearance and ther administration costs based on COVID-19 vaccine administration experience in the country.The total costs for acquisition and administration of nOPV during outbreak in Lower Middle Income countries including Tanzania, using different formulation and application/introduction	In countries with polio virus outbreak the the vaccine delivery is integrated into the Expanded Program of Immunization (EPI) at the operational level and service delivery follows the three-tiered structure of the health system, from peripheral to central levels including primary, secondary, and tertiary or specialized care.

[79] Ethiopia CCG. Contributing towards polio eradication in Ethiopia: AFP case detection and status of surveillance in pastoralist and semi-pastoralist communities of CORE Group Polio Project implementation districts (wordeas) in Ethiopia. Addis Ababa: CCRDA/CORE Group Ethiopia; 2012. https://coregroup.org/wpcontent/uploads/2017/08/Newborn_Tracking_of_OPV0_Final_FOR_PRINTING-1.pdf.

Criteria	Work Group Judgements	Evidence	Additional information
		approaches is estimated to be nOPV in oSIA $1.30 [43] Governments have to make decisions of whether to go for treatment of poliovirus patients, eradication or permanent control of polioviruses. The cost of treatment for Polioviruses patient ranges from $700 for lower income countries to $750,000 to higher income countries, $7000 for Lower to middle income countries including Tanzania[Error! Bookmark not defined.]. It is estimated that, the annual costs for a control strategy remains over $1 billion annually through 2042 and over $500 million through 2066. The projected cumulative cost savings for eradication of polio strategy compared to permanent control is $14 billion (range, $0–32 billion) in the year 2032[80].	
Equity			

[80] Marita Zimmermann , Brittany Hagedorn, and Hil Lyons, 2019. Projection of Costs of Polio Eradication Compared to Permanent Control. DOI: 10.1093/infdis/jiz488

Criteria	Work Group Judgements	Evidence	Additional information
What would be the impact of the intervention on health equity?	**PROBABLY NO IMPACT**	The IVD has clear data on target population to be vaccinated during the outbreak which is facilitated by a clear microplanning of the nOPV2 implementation	Emphasis has to be made to ensure universal coverage of target population to be vaccinated during an outbreak to ensure equity in the vaccination process.
Feasibility			
Is the intervention feasible to implement?	**YES**	The novel vaccine became the first vaccine to be submitted and approved by WHO Emergency Use Listing (EUL) under the revised procedure. Novel Oral Poliomyelitis Vaccine type 2 (nOPV2) has been granted time limited use under Emergency Use Listing procedure by WHO, on 13 November 2020. The TMDA has the Guidelines to be followed for the application of product which does qualify for normal registration procedure. In view of this, the approval procedure will use the Guidance on Processing Applications for registration of Medicinal Products through non-routine procedure in Tanzania, 1st Revision, March, 202081. TMDA will have to handle and finalize	Enhancement of surveillance during implementation to collect data to infrom on safety,efficacy and effectiveness of nOPV 2

[81] Made under Regulation 4 (1) of the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015

Criteria	Work Group Judgements	Evidence	Additional information
		internal administrative procedure to make sure the vaccine is made available in the Country for public use in case of outbreak. **Ability to evaluate:** The IVD programme has been implementing oPV3 vaccination very well with the coverage of 93%, 96%, 91%, 104 % and 74% respectively from year 2016 to 2020. Also, all health facilities in Tanzania are designated as AFP active surveillance sites. Hospitals and Health Centres are categorized as high and medium priority sites respectively depending on the possibility of the AFP case visiting the facilities. Therefore, implementation of nOPV2 will require the environmental surveillance, the country established Environmental Surveillance (ES) for Polio in April 2019. A total of fifteen sites were identified and visited to assess the eligibility of the sites in accordance with criteria. Four sites with closed drainage systems were established in three Councils of Dar es salaam region: Buguruni and Kipata sites in Ilala Councils, Mabibo site in Ubungo Council and	

Criteria	Work Group Judgements	Evidence	Additional information
		Msasani site in Kinondoni Council. Since establishment in 2019, all sites have been performing well above average and sample packed and transported under reverse cold chain to Uganda Virus Research Institute (UVRI) for testing. All the four sites have attained the target indicator for isolation of EV >50% [82].	

[82] https://www.afro.who.int/news/searching-polio-unusual-places-tanzania