RWANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP

(RWANDA-NITAG)

Rwanda NITAG Recommendation on the use of novel Oral Polio Vaccine type 2 (nOPV2) to respond to cVDPV2 outbreaks

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ACRONYMS

AFP	Acute Flaccid Paralysis
AEFI	Adverse Events Following Immunization
AESI	Adverse Event of special Interest
bOPV	Bivalent Oral Polio Vaccine
CCEOP	Cold Chain Equipment Optimization Platform
$CCID_{50}$	50% Cell Culture Infectious Dose
cDNA	complementary Deoxyribonucleic Acid
CI	Confidence Interval
cVDPV	circulating Vaccine Derived Polio Virus
DRC	Democratic Republic of the Congo
EUL	Emergency Use Listing
GPEI	Global Polio Eradication Initiative
HINARI	Health Internetwork Access to Research Initiative
IPV	Inactivated Polio Vaccine
MCH	Maternal and Child Health
MDVP	Multi-Dose Vial Policy
mOPV2	Monovalent Oral Polio vaccine type 2
NITAG	National Immunization Technical Advisory Group
nOPV	Novel Oral Polio Vaccine type 2
nOPV2-CD	Novel Oral Polio Vaccine type 2-Codon-deoptimized
OPV2	Oral Polio Vaccine Type 2
PCR	Polymerase chain reaction (PCR)
RNA	Ribonucleic acid
SAGE	Strategic Advisory Group of Experts
SIAs	Supplementary Immunization Activities
$TCID_{50}$	Medium Tissue Culture Infectious Dose
tOPV	Trivalent Oral Polio Vaccine
US$	United States Dollar
UTR	Sabin 5′ Untranslated Region
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VDPV	Vaccine-Derived Polio Virus
VVM	Vaccine Vial Monitor
WPV	Wild Poliovirus
WHO	World Health Organization

EXECUTIVE SUMMARY

The goal two of the Global Polio Eradication Initiative (GPEI) strategy for polio eradication 2022-2026 is to stop circulating Vaccine Derived Polio Virus (cVDPV) transmission and prevent outbreaks in non-endemic countries.

Approximately 90% of cVDPV outbreaks are caused by the type 2 strain of the Sabin vaccine, and this constitutes a great challenge to Polio eradication efforts.
The spread and continuation of current cVDPV2 outbreaks are driven by several factors, most notably declining mucosal immunity to type 2 virus among young children born after the switch; low essential immunization coverage with Inactivated Polio Vaccine (IPV); regional migration patterns that allow the virus to jump from one population to another; delays in detecting cVDPV2.

From 2020 to 2022 worldwide, 2384 cVDPV2 and 83 of cVDPV1 were isolated from Acute Flaccid Paralysis (AFP) cases while 1314 cVDPV2 and 93 cVDPV1 were detected from environmental samples. Only one case of cVDPV3 was reported from Israel. Out of 631 cVDPV2 events reported worldwide in 2022, 73.5% (464 cases) was reported from the African Region, with 50.4% of cases notified from Democratic Republic of the Congo (DRC). Recently, Burundi declared an outbreak of cVDPV2 after more than 30 years without polio circulation in the country. One case was isolated from AFP sample, 2 cases were confirmed from healthy contact children, and five cases were isolated from environmental surveillance.

The increasing number of cVDPV2 led to the withdrawal of OPV2 and the introduction of IPV in routine immunization. Two years after the cessation of the use of the type 2 Oral Polio Vaccine (OPV2), the number of cVDPV2 increased, and for some, the source was not well established. The use of mOPV2 to respond to cVDPV2 outbreaks led in some locations to the new outbreaks, raising concerns on the effective strategy to stop the cVDPV2 transmission and fully eradicate Polio.

To respond to this challenge, the GPEI partners have emphasized the need for developing more genetically stable OPVs and have accelerated the development and clinical testing of a novel OPV2 (nOPV2) that is a modified OPV2 and has a substantially lower risk of reversion to paralytic form that paralyzes children who have not been sufficiently immunized.

After several clinical trials, the nOPV2 was proven to be safe and immunogenic at the same level of OPV2. Based on these results, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization endorsed the use of nOPV2 as the vaccine of choice to respond to cVDPV2 outbreaks after the issuance of interim recommendation for Emergency Use Listing (EUL), the completion of the review of initial use period, and fulfillment of all requirements for its use.

To implement the WHO SAGE recommendation and as part of preparedness to respond to any potential cVDPV2, the Ministry of Health requested Rwanda National Immunization Technical Advisory Group (NITAG) to provide evidence-based recommendation on the use of nOPV2 under EUL in Rwanda to respond to cVDVP2 outbreaks. To respond to this request, NITAG produced the present technical dossier which includes recommendations to the Ministry of Health on the nOPV2 use in Rwanda.

Upon reception of the request, a technical working group was established and assigned task to collect and analyse available information to support the recommendation. From the available literature, relevant published and unpublished articles and reports related to the recommendation elements were analysed. Findings were summarized and the Rwanda NITAG concluded the following:

1. Outbreaks of type 2 cVDPV are a major challenge to achieve Polio eradication. These outbreaks are caused by the use of type 2 oral polio-containing vaccine such as mOPV2 and tOPV in outbreak response. Factors including low quality and delayed polio outbreak response as well as insufficient routine immunization coverage led to the declining of gut immunity to the type 2 virus in young children after countries switched from trivalent to bivalent oral polio vaccine (bOPV).
2. Even though Rwanda interrupted the polio transmission and was certified free from polio in 2004, the epidemiological situation of the cVDPV2 outbreak in Burundi and DRC, the geographical location, the importance of migration and population movement between countries and the protracted humanitarian crisis in DRC, put the Rwanda at high risk of cVDPV2 transmission. To prevent the spread into the country, polio supplementary immunization activities (SIAs) are required to enhance the population immunity.
3. The modification of Sabin 2 OPV provided a more genetically stable nOPV2 which has proven similar safety and immunogenicity ability to stop the transmission of cVDPV2. The vaccine has been recommended by WHO SAGE on immunization under Emergency Use Listing to respond to the cVDPV2 outbreaks.
4. The vaccine is affordable and logistically accommodable within the existing cold chain capacity. The immunization program is capacitated enough to deploy the vaccine at all delivery points in the country.
5. The Rwanda NITAG considered that relevant information was obtained to support the recommendation and advised the use of nOPV2 in the context of responding to the risk of cVDPV2 outbreaks in the country.

1. INTRODUCTION

1.1. Context of the request

Following the recommendation from World Health Organization (WHO) to use novel Oral Polio Vaccine type 2(nOPV2) to respond to circulating vaccine-derived poliovirus type 2 (cVDPV2), the Rwanda National Immunization Technical Advisory Group (Rwanda NITAG) received a request from the Ministry of Health, to review relevant evidence and advise on the use of nOPV2 vaccine in Rwanda to respond to cVDPV2 outbreaks.

1.2. Poliomyelitis disease and vaccination

Poliomyelitis (polio) is a highly infectious disease caused by the polio virus, an enterovirus that invades the nervous system. The human is the only source of transmission by person to person through excretion in feces and pharyngeal secretions, mainly via the hand-to-mouth route. The human cells and a few subhuman primate species have been seen expressing the poliovirus receptor concluding to a human reservoir for the virus.[1] The incubation period is commonly six to 20 days with a range of three to 35 days. About 95% of infected people are asymptomatic and can spread the virus and infect others. Paralysis is the most common complication observed from the infection and affects mostly the lower limbs. Paralysis of the respiratory muscles is rare but can be fatal. It has been estimated that less than 1% of primary poliovirus infections causes paralytic poliomyelitis. The polio infection is predominant among children aged 0-5 years old with more than 90% of the cases, however, anyone who is unvaccinated can contract the disease.[2,3,4]

The first candidate vaccines are the formalin-inactivated vaccine (IPV) developed by Jonas Salk in 1953 and the live-attenuated vaccines (OPV) developed by Albert Sabin in 1960 from attenuated strains of poliovirus; both were found suitable for human immunization considering that they provided good antibody levels while being less neurotropic. They were therefore selected and licensed between 1961 and 1963 in the United States for widespread use.[5,6]

After Polio vaccines were licensed, several countries introduced the vaccines in their immunization program since 1960. WHO has provided oversight of vaccines production and distribution in collaboration with national control authorities. Initially, separate monovalent vaccine for each serotype were given with sequential administration of types 1,2, and 3. Few years later, a trivalent

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[1] Nathanson, N., & Kew, O. M. (2010). From emergence to eradication: the epidemiology of poliomyelitis deconstructed. *American journal of epidemiology*, *172*(11), 1213-1229.

[2] Zucker, H. (2021). Poliomyelitis: Infantile Paralysis. African Journal of Medical Sciences, 6(3).

[3] LaForce, F. M., Lichnevski, M. S., Keja, J., & Henderson, R. H. (1980). Clinical survey techniques to estimate prevalence and annual incidence of poliomyelitis in developing countries. Bulletin of the World Health Organization, 58(4), 609.

[4] https://www.who.int/health-topics/poliomyelitis#tab=tab_1

[5] Horaud, F. (1993). Albert B. Sabin and the development of oral polio vaccine. Biologicals, 21(4), 311-316.

[6] Juskewitch, BA, J. E., Tapia, BA, C. J., & Windebank, A. J. (2010). Lessons from the Salk polio vaccine: methods for and risks of rapid translation. Clinical and translational science, 3(4), 182-185.

vaccine containing equal proportions of poliovirus types came into use, however, lower seroconversion rates of types 1 and 3 were reported. A balanced formulation of trivalent OPV which contained 10^6, 10^5, $10^{5.5}$ of 50% tissue culture infective dose (TCID50) was used to enhance the amount of type 3 virus. This improved the immunogenicity of the trivalent vaccine and the newly formulated vaccine, was, therefore, recommended by the Global Advisory Group. The OPV vaccine was easier to administrate and had a herd effect, inducing long-lasting protective systemic, humoral and cellular immunity as well as local mucosal resistance to poliovirus infection. In 1972, Sabin donated his vaccine strains of poliovirus to WHO which increased the availability of the vaccine to developing countries. From 1977 to 1995, the percentage of children who received the required three doses of OPV in the first years of life increased from 5% to 80% worldwide.[7]

Oral Polio Vaccine is recognized for its high immunogenicity after administration of three doses. However, evidence of its association with the occurrence of Vaccine-Associated Paralytic Poliomyelitis (VAPP) and Vaccine Derived Poliovirus strains (VDPV) has been demonstrated.[8,9] In areas with low levels of population immunity, the live weakened virus originally contained in OPV can genetically revert into a form that can cause paralysis. The virus then becomes known as circulating vaccine-derived poliovirus (cVDPV). Approximately 90% of cVDPV outbreaks are caused by the type 2 strain of the Sabin vaccine, and this causes a great challenge to polio eradication efforts[10]. Globally, the polio surveillance system detected 829 cVDPV cases in 2022, isolated from Acute Flaccid Paralysis (AFP) patients, of which 657 were cVDPV2 and 172 were cVDPV1. About 308 cVDPV2 cases were isolated from environmental surveillance.[11]

Although vaccination helped to reduce drastically the incidence of poliomyelitis, the persistence of cVDPV2 outbreaks despite vigorous outbreak response measures using mOPV2 is of concern. The use of this vaccine has raised questions as it could lead to more cVDPV2 cases if used in a population with poor immunity.[12] To respond to this challenge, the GPEI partners have emphasized the need for developing more genetically stable OPVs and have accelerated the development and clinical testing of nOPV2 which has a substantially lower risk of reversion to paralytic form that causes paralysis in children who have not been sufficiently immunized.[13] As nOPV2 offers the best alternative to the use of Sabin mOPV2 for outbreak responses, GPEI partners agreed that

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[7] Baicus A. History of polio vaccination. World J Virol 2012; 1(4):108-114 Available from: URL: http://www.wjgnet.com/2220-3249/full/v1/i4/108.htm DOI: http://dx.doi.org/10.5501/wjv.v1.i4.108

[8] Nkowane BM, Wassilak SGF, Orenstein WA, et al. Vaccine-Associated Paralytic Poliomyelitis: United States: 1973 Through 1984. JAMA. 1987;257(10):1335–1340. doi:10.1001/jama.1987.03390100073029

[9] Lauren R. Platt, Concepción F. Estívariz, Roland W. Sutter. Vaccine-Associated Paralytic Poliomyelitis: A Review of the Epidemiology and Estimation of the Global Burden, The Journal of Infectious Diseases, Volume 210, Issue suppl_1, November 2014, Pages S380–S389, https://doi.org/10.1093/infdis/jiu184

[10] Martin, J. (2022). Genetic characterization of novel oral polio vaccine type 2 viruses during initial use phase under emergency use listing—worldwide, March–October 2021. MMWR. Morbidity and Mortality Weekly Report, 71.

[11] Polio surveillance update, week 52, 2021 (unpublished)

[12] Macklin, G. R., Goel, A. K., Mach, O., Tallis, G., Ahmed, J. A., O'Reilly, K. M., ... & Diop, O. M. (2022). Epidemiology of type 2 vaccine-derived poliovirus outbreaks between 2016 and 2020. Vaccine.

[13] Wahid, R., Mercer, L., Gast, C., De Leon, T., Sáez-Llorens, X., Fix, A., ... & Konz, J. O. (2022). Evaluating stability of attenuated Sabin and two novel type 2 oral poliovirus vaccines in children. npj Vaccines, 7(1), 19.

nOPV2 should be broadly replace Sabin mOPV2 in outbreak response to prevent seeding of new cVDPV2 emergencies.[14] Genetically more stable nOPV1 and nOPV3 vaccines are also under accelerated development in the framework of eradicating all VDPVs, however, the success or failure may remain on how well genetically more stable nOPVs will perform.

The nOPV2 was found to be a potentially significant tool to help stop outbreaks more sustainably. In December 2020, the WHO released a recommendation for an Emergency Use Listing (EUL) of nOPV2 and recommended its use for cVDPV2 outbreak response.[15]

Given the WHO recommendation, the Rwanda Ministry of Health has requested NITAG to advise whether nOPV2 should be used in the country under EUL to respond to cVDVP2 outbreaks. The present technical dossier was therefore produced to provide evidence-based recommendations to the Ministry of Health on the use of nOPV2 in Rwanda.

2. METHODS

The Rwanda NITAG held its meeting on 12 April 2023 to address the question "Should nOPV2 be used in the Rwanda population in response to cVDPV2 outbreaks?" To answer the question the Rwanda NITAG established a working group which worked on different elements of the recommendation. The document was also reviewed by all members online. The members defined the following steps for the development of the recommendation:

1. Identify and define the basic elements guiding the elaboration of the recommendations
2. Frame the questions for the interventions which are part of the recommendation
3. Determine sources of evidence and apply literature search strategies
4. Identify publications, pertinent studies, published and unpublished reports/articles of interest
5. Assess the quality of articles retained considering the methods and materials used to conduct the study.

Five elements were analysed and where applicable, PICO (Population, Intervention, Comparator, Outcome) methods were applied to frame the research question. The following elements served as a basic framework to develop the recommendation:

- Epidemiology of Wild Polio Virus (WPV) and cVDPV2
- Immunogenicity and safety of nOPV2
- Vaccine characteristics, logistic, handling, and administration
- Existing alternative interventions to respond to cVDPV2 outbreaks
- Economic and operational considerations of the use of nOPV2

[14] Macklin, G. R., Peak, C., Eisenhawer, M., Kurji, F., Mach, O., Konz, J., ... & nOPV2 Working Group. (2022). Enabling accelerated vaccine roll-out for public health emergencies of international concern (PHEICs): novel oral polio vaccine type 2 (nOPV2) experience. Vaccine.

[15] Recommendation for an Emergency Use Listing (EUL) of novel Oral Polio Vaccine type 2 (nOPV2) submitted by PT BIOFARMA (PERSERO), available at: https://extranet.who.int/pqweb/sites/default/files/documents/nOPV2_EUL_recommendation_0.pdf

The formulation of the questions on the use of nOPV2 was based on the elements of the recommendation cited above:

1. What is the burden of cVDPV2 at the global, regional, and national levels?
2. What is the immunogenicity and safety profile of nOPV2?
3. What are the vaccine characteristics, logistic, cold chain, handling, and administration requirements?
4. Are there other alternatives to respond to cVDPV2 outbreaks?
5. What are the economic and operational considerations for the use of nOPV2 in response to cVDPV2 outbreaks?

2.1 Documentation sources of evidence and strategies used for the literature search

A number of databases were consulted including the Global NITAG Network website, Health Internetwork Access to Research Initiative (HINARI), Google Scholar, GPEI, and WHO resources. The relevant articles published, and unpublished reports were selected for inclusion in the final methodological analysis. The keywords used for the literature search are summarized in the table below:

Questions	Keywords
1	Epidemiology-Progress towards Polio eradication- cVDPV2
2	Stability-Immunogenicity-Efficacy-Safety-nOPV2-effectiveness nOPV2
3	nOPV vaccine-Characteristics-storage conditions-administration
4	cVDPV2-outbreaks-vaccination campaign mOPV2-cVDPV2-mOPV2
5	Price mOPV2-nOPV2, GPEI- financing-budgeting -cVDPV2 response

2.2 Identification of potential articles and relevant studies

The relevant published and unpublished articles and reports were selected for inclusion the final methodological analysis. The team went through and numbered the articles according to the questions listed above, and a summary of the findings of each article was made.

Question	Number of articles
Epidemiological of Wild Polio Virus (WPV) and cVDPV2	13
Immunogenicity and safety of nOPV2	10
Vaccine characteristics, logistic, handling, and administration	3
Other alternatives to respond to the cVDPV2 outbreak	6
Economic and operational considerations for the use of nOPV2 in response to cVDPV2 outbreaks	3

3. FINDINGS FROM THE EVIDENCE

The findings from the search were summarized in the following sections

3.1 Epidemiology of Poliomyelitis

In 1988, the annual global burden of paralytic poliomyelitis was estimated to be >350 000 cases, with wild poliovirus (WPV) transmission reported in more than 125 countries.[16] Increasing epidemics during the late 19th and 20th centuries lead to the initiation of a worldwide global effort for polio eradication in 1988. This resulted in the creation of GPEI super headed by WHO and various other organizations.[17] The efforts of the GPEI resulted in the intensified polio vaccination campaign, routine immunization, and surveillance. This led to more than a 99% reduction of wild poliovirus cases worldwide while the total number of polio-endemic countries dropped from 24 in 2000 to two in 2022; namely Afghanistan and Pakistan.[18,19] Wild poliovirus type 2 and type 3 were interrupted globally and the certification of eradication of the two strains was published in 2015 and 2019 respectively.[20] From 2016 to date, Afghanistan and Pakistan remain the two countries which are still reporting wild poliovirus type 1 cases. African Region was certified to have eradicated all the types of polioviruses in August 2020.[21]

[16] World Health Organization, Polio vaccines position paper, Weekly epidemiological record, No 12, 2016, 91, 145–168

[17] Aylward, B., & Tangermann, R. (2011). The global polio eradication initiative: lessons learned and prospects for success. Vaccine, 29, D80-D85.

[18] Anjum, S., Chaudry, N., Arif, S., & Ahmad, T. (2014). Epidemiological Characteristics of Poliomyelitis During the 21st Century (2000-2013). International Journal of Public Health Science, 3(3), 7187

[19] World Health Organization. (2021). Progress towards polio eradication–worldwide, January 2019–June 2021–. Weekly Epidemiological Record, 96(34), 393-400.

[20] Dyer, O. (2019). Polio: WHO declares type 3 poliovirus eradicated after 31-year campaign. BMJ: British Medical Journal (Online), 367.

[21] World Health Organization. (2022). Progress towards polio eradication–worldwide, January 2020–April 2022–. Weekly Epidemiological Record, 97(23), 249-257.

Though polio type 2 and 3 have been eradicated globally and the incidence of WPV1 dramatically reduced, the emerging cVDPVs constitutes a significant barrier to eradication efforts.[22] The OPVs contain a live, weakened form of poliovirus which, on rare occasions, can replicate in the human gastrointestinal tract and genetically changes. As these viruses spread from person to person, further changes occur and if the spread continue in a poorly immunized population and especially in areas where there is poor hygiene, poor sanitation, or overcrowding, it may genetically modify over time and regains the ability to cause paralysis, giving rise to a cVDPV. Evidence shows that low polio immunization coverage is the key risk factor for the emergence and spread of a cVDPV.[23,24]

The VDPV strains continued to circulate in more than 20 countries in recent years. From 2020 to 2022, 2384 cVDPV2 and 83 of cVDPV1 were isolated from AFP cases while 1314 cVDPV2 and 93 cVDPV1 were detected from environmental samples. Only one case of cVDPV3 was reported from Israel.[25] Out of 631 cVDPV2 events reported in 2022, 73.5% (464 cases) was reported from the African Region, with 50.4% of cases notified from Democratic Republic of the Congo (DRC).[26] In March 2023, Burundi declared an outbreak of cVDPV2 after more than 30 years without polio circulation in the country. One case was isolated from AFP sample, 2 cases were confirmed from healthy contact children, and five cases were isolated from environmental surveillance.[27]

The global increase of cVDPV2 cases led to the withdrawal of OPV2 and the introduction of Inactivated Polio Vaccine (IPV) in routine immunization.[28] Two years after the cessation of OPV2 use, the number of cVDPV2 continued to increase. The use of mOPV2 to respond to cVDPV2 outbreaks led in some locations to the new outbreaks, raising concerns on the effective strategy to stop the cVDPV2 transmission and fully eradicate Polio. [29,30]

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[22] Lai, Y. A., Chen, X., Kunasekaran, M., Rahman, B., & MacIntyre, C. R. (2022). Global epidemiology of vaccine-derived poliovirus 2016–2021: a descriptive analysis and retrospective case-control study. EClinicalMedicine, 50, 101508.

[23]Wringe, A., Fine, P. E., Sutter, R. W., & Kew, O. M. (2008). Estimating the extent of vaccine-derived poliovirus infection. PLoS One, 3(10), e3433.

[24] Kew, O. M., Wright, P. F., Agol, V. I., Delpeyroux, F., Shimizu, H., Nathanson, N., & Pallansch, M. A. (2004). Circulating vaccine-derived polioviruses: current state of knowledge. Bulletin of the World Health Organization, 82, 16-23

[25] World Health Organization, Acute Flaccid Paralysis and Environmental surveillance in the East and Southern Africa [unpublished], 2020-2022

[26] World Health Organization, Acute Flaccid Paralysis and Environmental surveillance in the East and Southern Africa [unpublished], Week 11, 2023

[27] https://www.afro.who.int/countries/burundi/news/burundi-declares-outbreak-circulating-poliovirus-type-2

[28] Global Polio Eradication Initiative (GPEI): Polio Endgame Strategy, 2013-2018

[29] Harutyunyan, V., Quddus, A., Pallansch, M., Zipursky, S., Woods, D., Ottosen, A., ... & Lewis, I. (2023). Global oral poliovirus vaccine stockpile management as an essential preparedness and response mechanism for type 2 poliovirus outbreaks following global oral poliovirus vaccine type 2 withdrawal. Vaccine, 41, A70-A78.

[30] Kalkowska, D. A., Wassilak, S. G., Pallansch, M. A., Burns, C. C., Wiesen, E., Durry, E., ... & Thompson, K. M. (2022). Outbreak response strategies with type 2-containing oral poliovirus vaccines. Vaccine.

The global Polio eradication strategy 2022-2026, emphasizes on working on an emergency foundation to ensure rapid case detection and strong outbreak response to quickly stop transmission of cVDPV2 and minimize the risk of seeding new emergences. The plan highlights the deployment of nOPV2 to minimize outbreak seeding as one of the new approaches to stop cVDPV2 along with improved surveillance, outbreak response speed, quality, political commitment, and community engagement.[31]

3.2 Immunogenicity and safety of nOPV2

The current immunization schedule includes bivalent OPV (bOPV) against type 1 and type 3, and at least one dose of IPV. However, IPV is not indicated for outbreak response because the vaccine does not induce mucosal immunity in persons without prior OPV immunization for the corresponding serotype; failing to stop onward transmission of the virus if infected children have not previously exposed to OPV vaccination.[32] It was imperative to modify the mOPV2 to a safer and more genetically stable vaccine capable of inducing high immunogenicity against cVDPV2.

The Sabin OPV2 was redesigned to the attenuated neurovirulent vaccine by codon deoptimization (nOPV2- Codon-deoptimized) to eliminate the ability of the virus to revert by single nucleotide changes within the main Sabin OPV2. The method consisted of codon deoptimization of the capsid region, combined with stabilization of known attenuation determinants in the Sabin 5′ untranslated region (UTR), to engineer a nOPV2 strain that is genetically stable.[33]

To test the immunogenicity, mice were inoculated intraperitoneally with a range of doses of either Sabin OPV2, or nOPV2- codon-deoptimized (nOPV2-CD) and sera were collected after 21 days. The measure of neutralizing antibody titers showed that nOPV2-CD produced a dose-dependent neutralizing antibody response that was equivalent to that of Sabin OPV2, providing preclinical evidence that nOPV2-CD replicated effectively, presented antigen, and elicited an antibody response.[34]

Based on the pre-clinical trial results of the immunogenicity of nOPV2 in the mice, a phase one human clinical trial was performed to assess the safety, immunogenicity, and genetic stability of nOPV2. This phase I trial involved 30 adult volunteers, previously immunized with inactivated poliovirus vaccine (IPV). Each volunteer received 10^6 50% cell culture infectious dose units ($CCID_{50}$) of the virus by oral administration. Analysis of shed virus in stool samples showed effective intestinal mucosal replication of the vaccine virus in all vaccinees. Importantly, vaccination with nOPV2 elicited a significant increase in neutralizing antibody titers against type

[31] World Health Organization, & Global Polio Eradication Initiative. (2021). Polio eradication strategy 2022–2026: delivering on a promise.

[32] Macklin, G. R., Grassly, N. C., Sutter, R. W., Mach, O., Bandyopadhyay, A. S., Edmunds, W. J., & O'Reilly, K. M. (2019). Vaccine schedules and the effect on humoral and intestinal immunity against poliovirus: a systematic review and network meta-analysis. The Lancet Infectious Diseases, 19(10), 1121-1128.

[33] Konopka-Anstadt, J. L., Campagnoli, R., Vincent, A., Shaw, J., Wei, L., Wynn, N. T., ... & Burns, C. C. (2020). Development of a new oral poliovirus vaccine for the eradication end game using codon deoptimization. npj Vaccines, 5(1), 2

[34] Te Yeh, M., Bujaki, E., Dolan, P. T., Smith, M., Wahid, R., Konz, J., ... & Andino, R. (2020). Engineering the live-attenuated polio vaccine to prevent reversion to virulence. Cell host & microbe, 27(5), 736-751.

2 poliovirus in at least 83% of the subjects. An anamnestic antibody response was evident with a boost in neutralizing antibodies titers of more than eightfold. Reversion to neurovirulence was low in isolates from those vaccinated with both candidates, and sequencing of shed virus indicated that there was no loss of attenuation in the primary site of reversion in Sabin OPV2.[35]

The following randomized clinical trial was conducted in Belgium to assess and compare the safety up to 28 days after each dose, and immunogenicity between monovalent OPV2 and the two novel OPV2 candidates. The study involved healthy adults previously vaccinated with at least three polio vaccinations including OPV or IPV. The trial was implemented in two phases including a phase 4 "historical control" study of mOPV2 done before the global withdrawal of OPV2, and the second was a phase 2 study with novel OPV2-c1 and novel OPV2-c2. Eligible participants were healthy adults aged 18–50 years. In the historical control trial, 100 volunteers were enrolled and were randomly assigned to either one dose (50 participants) or two doses (50 participants) of mOPV2. In the novel OPV2 trial, 200 adults with previous OPV vaccinations were recruited and assigned to the four groups to receive one or two doses of novel OPV2-c1 or novel OPV2-c2 (n=50 per group); a further 50 participants, previously vaccinated with IPV, were assigned to novel OPV2-c1 (n=17), novel OPV2-c2 (n=16), or placebo (n=17). After the first doses in previously OPV-vaccinated participants, 62 (62%) of 100 mOPV2 recipients, 71 (71%) of 100 recipients of novel OPV2-c1, and 74 (74%) of 100 recipients of novel OPV2-c2 reported adverse events, of which nine were considered severe. In IPV-vaccinated participants, adverse events occurred in 16 (94%) of 17 who received nOPV2-c1 and 13 (81%) of 16 who received nOPV2-c2, compared with 15 (88%) of 17 placebo recipients. In this group of IPV-vaccinated individuals, four severe events were reported. In previously OPV-vaccinated participants, 286 (97%) of 296 were seropositive at baseline; after one dose, 100% of nOPV2 vaccinees and 97 (97%) of mOPV2 vaccinees were seropositive.[36]

After preliminary evaluation and confirmation of the safety and immunogenicity of nOPV2 in comparison with mOPV2 in larger adult studies, subsequent trials were conducted to confirm the efficacy and safety of nOPV2 compared with that of mOPV2 in fully immunized young children and in infants. The objectives were to assess safety in all participants and non-inferiority of nOPV2 seroprotection versus mOPV2 in infants (non-inferiority margin 10%). Two single-centre, multi-site, partly-masked, randomized trials in healthy cohorts of children (aged 1–4 years) and infants (aged 18–22 weeks) were designed and implemented in Panama including a control phase 4 study with monovalent Sabin OPV2 and a phase 2 study with low and high doses of two novel OPV2 candidates. The study enrolled 110 and 574 children for phase 4 control and phase 2 study respectively, with a documented history of complete polio immunization with either tOPV or IPV.

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[35] 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.

[36] De Coster, I., Leroux-Roels, I., Bandyopadhyay, A. S., Gast, C., Withanage, K., Steenackers, K., ... & Van Damme, P. (2021). 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, 397(10268), 39-50.

All participants received one OPV2 vaccination and subsets received two doses 28 days apart. Parents were requested to report any adverse event. Type 2 poliovirus neutralizing antibodies were measured at days 0, 7, 28, and 56, and stool viral shedding was assessed up to 28 days post-vaccination. Vaccinations were safe and well tolerated with no causally associated serious adverse events or important medical events. Solicited and unsolicited adverse events were overwhelmingly mild or moderate irrespective of vaccine or dose. Almost all children were seroprotected at baseline, indicating high baseline immunity. In children, the seroprotection rate 28 days after one dose was 100% for mOPV2 and both nOPV2 candidates. In infants at day 28, 91 (94% [95% CI 87–98]) of 97 were seroprotected after receiving mOPV2, 134 (94% [88–97]) of 143 after high-dose nOPV2-c1, 122 (93% [87–97]) of 131 after low-dose nOPV2-c1, 138 (95% [90–98]) of 146 after high-dose nOPV2-c2, and 115 (91% [84–95]) of 127 after low-dose nOPV2-c2. Non-inferiority was shown for low-dose and high-dose nOPV2-c1 and high-dose nOPV2-c2 despite mOPV2 recipients having higher baseline immunity.[37]

Safety, immunogenicity, and fecal shedding of nOPV2 were also tested in poliovirus vaccine-naive infants, in a randomized, double-blind, controlled, phase 2 trial that was conducted in Bangladesh and involved healthy newborn. The objective was to evaluate the safety, immunogenicity, and fecal shedding of nOPV2. Two groups of infants were randomly assigned (2:1) to receive either two doses of nOPV2 or a placebo. The vaccine or placebo were administered at age 0–3 days and at 4 weeks. The primary safety outcome was safety and tolerability after one and two doses of nOPV2, given 4 weeks apart and the primary immunogenicity outcome was the seroconversion rate for neutralizing antibodies against type 2 poliovirus, measured 28 days after the first and second vaccinations with nOPV2. Adverse events were recorded, and poliovirus neutralizing antibody responses were measured in sera drawn at birth and at age 4 weeks and 8 weeks. The trial documented a seroconversion rate of 90% by week 8 after two doses and 99% of infants had seroprotective antibodies. The study results concluded that nOPV2 was well tolerated and immunogenic in newborn infants, with two doses, at birth and 4 weeks, resulting in almost 99% of infants having protective neutralizing antibodies.[38]
Subsequent clinical trials were carried out to test the safety and immunogenicity of nOPV2 among adults, children, and infants. These studies documented good safety and immunogenicity profiles of nOPV2.[39,40]

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[37] Sáez-Llorens, X., Bandyopadhyay, A. S., Gast, C., De Leon, T., DeAntonio, R., Jimeno, J., ... & Rüttimann, R. (2021). 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, 397(10268), 27-38.
[38] Zaman, K., Bandyopadhyay, A. S., Hoque, M., Gast, C., Yunus, M., Jamil, K. M., ... & Tritama, E. (2023). Evaluation of the safety, immunogenicity, and faecal shedding of novel oral polio vaccine type 2 in healthy newborn infants in Bangladesh: a randomised, controlled, phase 2 clinical trial. The Lancet, 401(10371), 131-139.

[39] De Coster, I., Leroux-Roels, I., Bandyopadhyay, A. S., Gast, C., Withanage, K., Steenackers, K., ... & Van Damme, P. (2021). 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, 397(10268), 39-50

[40] Sáez-Llorens, X., Bandyopadhyay, A. S., Gast, C., De Leon, T., DeAntonio, R., Jimeno, J., ... & Rüttimann, R. (2021). 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, 397(10268), 27-38.

In the framework of evaluating the nOPV2 immunogenicity in outbreak response settings, a serological survey was conducted in Tajikistan. The objective was to provide a rapid evaluation of nOPV2 immunogenicity achieved in vaccination campaign settings. Type 2 polio antibodies were measured in children who were reported to have received two doses of nOPV2. About 236 children were enrolled and seroprevalence tests were performed before nOPV2, after one and two doses. The analysis indicated that type 2 antibody seroprevalence was 26% (53/204; 95% CI: [20-33]) before nOPV2, 77% (161/210; 95% CI: [70-82]), and 83% (174/209; 95% CI: [77-88]) after one and two doses respectively. The increase in seroprevalence was statistically significant (51 percentage points [42-59], $p<0{\cdot}0001$) between baseline and after one dose but not between the first and second doses (6 percentage points [2-15], $p=0{\cdot}12$). Seroconversion from the first nOPV2 dose, 67% (89/132; 95% CI: 59-75), was significantly greater than that from the second nOPV2 dose, 44% (20/45; 95% CI: 30-60; χ^2 $p=0{\cdot}010$). Total seroconversion after two nOPV2 doses was 77% (101/132; 95% CI: 68-83). [41]

The Global Advisory Committee on Vaccine Safety (GACVS) evaluated safety data from Nigeria which vaccinated more than 88 million using nOPV2 in the context of outbreak response between March and October 2021, documented 6 adverse events of special interest (AESIs) being consistent with a causal association with immunization. There were 3 cases of suspected vaccine-associated paralytic poliomyelitis (VAPP), and one each of anaphylaxis, allergic reaction, and meningoencephalitis. The reporting rates for these events were all well below the expected range, so did not generate any new safety signals.[42]

3.3 Vaccine characteristics, logistic, handling, and administration requirements

3.1.1 Vaccine characteristics

The nOPV2 is a live attenuated Poliomyelitis virus type 2 modified from the Sabin strain prepared in Vero cells derived from African green monkey kidney. The nOPV2 strain S2/cre5/S15domV/rec1/hifi3 is derived from a modified Sabin-2 infectious cDNA clone. The vaccine is a clear liquid with a slightly yellow to light red color due to the presence of phenol red used as a pH indicator. The vaccine is presented in 50 and each vial contains the volume necessary to deliver 50 doses ($\geq$ 100 drops; 1 dose = 2 drops = 0.1 ml).[43]

3.1.2 Vaccine storage and handling

The nOPV2 50 doses (oral) bears a Vaccine Vial Monitor (VVM2) affixed on the label of the vaccine vial. The assigned shelf life of nOPV2 50 doses is currently 12 months when stored at

[41] Mirzoev, A., Macklin, G. R., Zhang, Y., Mainou, B. A., Sadykova, U., Olsavszky, V. S., ... & Mach, O. (2022). Assessment of serological responses following vaccination campaigns with type 2 novel oral polio vaccine: a population-based study in Tajikistan in 2021. The Lancet Global Health, 10(12), e1807-e1814.

[42] World Health Organization. (2022). Report from the first joint meeting (virtual) of WHO Global Advisory Committee on Vaccine Safety and WHO Advisory Committee on Safety of Medicinal Products, 14–16 June 2022. Weekly Epidemiological Record, 97(34), 397-407.

[43] WHO (2020). Recommendation for an Emergency Use Listing (EUL) of Novel Oral Polio Vaccine Type 2 (nOPV2)

minus 20°C. It can also be stored for up to 3 months between +2° C and +8° C. These storage periods can be revised upon the provision of additional supportive stability data. The nOPV2 use under EUL requires strict stock management practices and accurate storage and transaction records at all supply chain. The GPEI guidelines on nOPV2 management provide further guidance on the storage and vaccine handling.[44]

3.1.3 Indication, contra-indications, and administration requirements

The nOPV2 is indicated for all age groups for emergency use in response to outbreaks caused by type 2 poliovirus when and where it is required by the GPEI or WHO. The vaccine should not be administered to pregnant women and those with primary immune deficiency disease or suppressed immune response from medication, leukemia, lymphoma, or generalized malignancy.[45]

The nOPV2 is shed in the stool and possibly in the saliva of vaccine recipients. Transmission of the vaccine virus to close contacts is possible and is likely to be no greater and possibly less than that of Sabin2.

Two drops (0.1 ml containing $\geq 10^5$ $CCID_{50}$ infective units of type 2 poliovirus are delivered directly into the mouth from the multi-dose vial by dropper or dispenser. WHO Multi-dose Vial Policy (MDVP) is applicable to nOPV2 from which one or more doses of vaccine may be used in subsequent immunization sessions for up to a maximum of 4 weeks if all the conditions highlighted by the MDVP are met.[46]

In routine immunization, traditional oral polio vaccines are co-administered with other childhood vaccines. The nOPV2 is still recommended for use in the response to cVDPV2 outbreaks, its use in routine immunization is not yet endorsed. No contraindication to co-administration with other vaccines has been documented.[47]

3.4 Other alternatives to respond to cVDPV2

The cessation of tOPV from routine use was effective in 2016 by switching from t-OPV to b-OPV. Since the switch, the cVDPV2 spread has been larger and more rapid than would be assumed based on patterns of spread observed in cVDPV2 outbreaks prior to 2016, irrespective of routine immunization coverage.[48] The use of monovalent OPV2 (mOPV2) was the only strategy to control the transmission of cVDPV2 in affected areas. A stockpile of mOPV2 was created to respond to

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[44] GPEI (2022). Cold Chain and Vaccine Management Requirements in the Context of nOPV2 Use.

[45] https://extranet.who.int/pqweb/sites/default/files/documents/nOPV2_EUL_recommendation_0.pdf

[46] World Health Organization (2014). Policy Statement: Multi-dose Vial Policy. Handling of multi-dose vaccine vials after opening

[47] https://polioeradication.org/wp-content/uploads/2020/10/nOPV2-FAQ_EN_Oct-2020.pdf

[48] Bigouette, J. P., Wilkinson, A. L., Tallis, G., Burns, C. C., Wassilak, S. G., & Vertefeuille, J. F. (2021). Progress toward polio eradication—worldwide, January 2019–June 2021. Morbidity and Mortality Weekly Report, 70(34), 1129.

potential poliovirus type 2 (PV2) outbreaks and events.[49] However, it is evident that the Sabin 2 strains in mOPV2 are genetically unstable and could evolve and regain virulence through the reversion of key attenuating mutations. The emergence of new cVDPV2 cases after the use of mOPV2 in outbreak response areas has been documented. In addition, the challenges of cVDPV2 outbreaks in new areas without prior exposure to OPV2 required further use of the vaccine.[50] To minimize the transmission and risk of cVDPV2 outbreaks, vaccination response using mOPV2 should be large enough to cover populations infected with the outbreak virus, but small enough to avoid unnecessary exposure to mOPV2 which can seed a new outbreak. Thus, balancing the use of mOPV2 and the requirements to reduce the risk of cVDPV2 is very challenging.[51]
Referring to clinical trials results on the safety and immunogenicity, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization endorsed the use of nOPV2 as the vaccine of choice for response to cVDPV2 outbreaks after the interim recommendation for EUL is issued, and after review of the initial use period is completed and all requirements for use are met[52]. The clinical trials and field use have demonstrated that nOPV2 is safe and effective in protecting against type 2 poliovirus while decreasing the likelihood of cVDPV2 emergence in low immunity settings, This makes nOPV2 a vaccine of choice for cVDPV2 outbreak response.[53]

3.5 Economic and operational considerations for the use of nOPV2 in response to cVDPV2

The nOPV2 use is being recommended to respond to cVDPV2 outbreaks. The vaccine is not yet recommended for routine immunization. The production of nOPV2 is expected to be like production of mOPV2, which costs US$ 0.15 per dose. This means that over the long term, prices for nOPV2 could approach those for mOPV2.[54]

The Bill & Melinda Gates Foundation has funded the development of nOPV2 to date, working closely with GPEI partners throughout the process to ensure resources are going toward a tool that could prove critical to helping end all forms of poliovirus.[55] Based on the promising data from clinical trials, and the public health emergency that cVDPV2 constitutes, the Foundation pre-

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[49] Harutyunyan, V., Quddus, A., Pallansch, M., Zipursky, S., Woods, D., Ottosen, A., ... & Lewis, I. (2023). Global oral poliovirus vaccine stockpile management as an essential preparedness and response mechanism for type 2 poliovirus outbreaks following global oral poliovirus vaccine type 2 withdrawal. Vaccine, 41, A70-A78

[50] Kalkowska, D. A., Pallansch, M. A., Wassilak, S. G., Cochi, S. L., & Thompson, K. M. (2021). Serotype 2 oral poliovirus vaccine (OPV2) choices and the consequences of delaying outbreak response. Vaccine.

[51] Voorman, A., O'Reilly, K., Lyons, H., Goel, A. K., Touray, K., & Okiror, S. (2021). Real-time prediction model of cVDPV2 outbreaks to aid outbreak response vaccination strategies. Vaccine.

[52] https://cdn.who.int/media/docs/default-source/immunization/sage/2020/highlights-from-the-sage-october-2020-meeting_final.pdf?sfvrsn=bbad9d7_1

[53] Wahid, R., Mercer, L., Gast, C., De Leon, T., Sáez-Llorens, X., Fix, A., ... & Konz, J. O. (2022). Evaluating stability of attenuated Sabin and two novel type 2 oral poliovirus vaccines in children. npj Vaccines, 7(1), 19.

[54] https://polioeradication.org/wp-content/uploads/2022/10/nOPV2-FAQ-August-2022-EN.pdf

[55] https://www.gatesfoundation.org/ideas/media-center/press-releases/2022/10/world-health-summit-gates-foundation-commits-over-one-billion-to-end-polio

funded the production of 200 million doses of nOPV2 to enable its rapid deployment upon receiving EUL. GPEI supports countries for the vaccine rollout in the response to cVDPV2 in the framework of Polio eradication.[56]

Regarding vaccine logistics and delivery operations, the Rwanda Ministry of Health has strengthened its storage capacity at all levels of immunization delivery. The current storage capacity is sufficient to accommodate nOPV2 once supplied. In all district hospitals, the storage capacity usable is far superior to that required. The vaccine logistic and supply management has also been strengthened over the years as the country has been implementing Cold Chain Equipment Optimization Platform (CCEOP) strategy which allowed the vaccine to reach all the vaccination delivery points in optimal cold chain conditions.

As the vaccine is administered through the mouth and doesn't require specific handling procedures than those in place, the vaccine delivery will be integrated with the existing immunization delivery system.

Rwanda has been strengthening its capacity for safety surveillance including active and passive surveillance as well as AEFI investigation and causality assessment. Polio surveillance is integrated with the national program of disease surveillance and response. Enhancing vaccine safety and polio surveillance will require refresher trainings of Health Care Workers to ensure active AEFI surveillance, AFP active case search, and environmental surveillance to timely detect any serious AEFI and cVDPV2 cases. Wherever possible, the nOPV2 vaccination campaign will be integrated with other health interventions such as Maternal and Child Health (MCH) campaigns to ensure the efficient use of resources.

4. CONCLUSION AND RECOMMENDATION

4.1 Conclusion

The Outbreaks of cVDPV2 which account for most of the cVDPV cases globally are a major challenge to achieve Polio eradication. These outbreaks are driven by several factors, including low quality and delayed polio outbreak response as well as insufficient routine immunization coverage.

Rwanda interrupted polio transmission and was certified free from polio in 2004. To date, the country did not report any case of cVDPV. However, given the epidemiological situation in Burundi and DRC, the Rwanda geographical location, the importance of migration and population movement between these countries; the protracted humanitarian crisis in DRC which leads to influx of refugees, the risk of importation of cVDPV2 is high. This requires the country to enhance population immunity to prevent the outbreak.

The OPV2 has been modified to a safer and more genetically stable nOPV2 with similar immunogenicity ability to stop the transmission of cVDPV2. The vaccine has been recommended for cVDPV2 outbreak response by WHO SAGE on immunization under Emergency Use Listing. The vaccine is affordable and logistically accommodable within the existing cold chain capacity.

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[56] GPEI. Standards Operating Procedures for Responding to a poliovirus event or outbreak, 2022

4.2 Rwanda NITAG Recommendation

In view of the evidence above, Rwanda NITAG recommends the following:

1. The nOPV2 should be used for cVDPV2 outbreak response targeting children below 15 years old.
2. Vaccination coverage and monitoring mechanisms should be enhanced to ensure coverage above 95% during SIAs
3. Strengthen the safety surveillance system to ensure Adverse Events Following Immunization (AEFIs), Adverse Events of Special Interest (AESIs), and signals are timely detected, notified, investigated, and assessed for causality
4. Enhance AFP surveillance and active case search to timely detect and investigate any case of cVDPV2 or /and VAPP.
5. Enhance community mobilization and engagement to create high demand and vaccine uptake

Appendix2: Recommendation framework

EVIDENCE TO RECOMMENDATION FRAMEWORK
Question: Should nOPV2 be used in Rwanda population in response to VDPV2? **Population:** 0 to 15 years old **Intervention:** Two doses of nOPV2 **Comparison:** Other OPV2 **Outcome:** Reduced incidence of cVDPV2
Background Circulating Vaccine derived Polio Virus (cVDPV) remains a big challenge to the Global eradication of Polio. The spread and continuation of current cVDPV2 outbreaks are driven by several factors, most notably declining mucosal immunity to type 2 virus among young children born after the switch; low essential immunization coverage with IPV; regional migration patterns that allow the virus to jump from one population to another; delays in detecting cVDPV2. From 2020 to 2022, 2384 cVDPV2 and 83 of cVDPV1 were isolated from AFP cases while 1314 cVDPV2 and 93 cVDPV1 were detected from environmental samples. Only one case of cVDPV3 was reported from Israel. Out of 631 cVDPV2 events reported in 2022, 73.5% (464 cases) was reported from the African Region, with 50.4% of cases notified from Democratic Republic of the Congo (DRC). Recently, Burundi declared an outbreak of cVDPV after more than 30 years without polio circulation in the country. One case was isolated from AFP sample, 2 cases were confirmed from healthy contact children, and five cases were isolated from environmental surveillance. The increasing number of cVDPV2 led to the withdrawal of OPV2 and the introduction of Inactivated Polio Vaccine (IPV) in routine immunization. Two years after the cessation of OPV2 use, the number of cVDPV2 increased, and for some, the source was not well established. The use of mOPV2 to respond to cVDPV2 outbreaks led in some locations to the new outbreaks, raising concerns on the effective strategy to stop the cVDPV2 transmission and fully eradicate Polio. To respond to this challenge, a type 2 novel Oral Polio Vaccine (nOPV2) that is a modified OPV2 was developed and has a substantially lower risk of reversion to paralytic form that causes paralyzes children who have not been sufficiently immunized.

Element	Specific data	Evidence	Ranking	Additional information
Vaccine Safety and efficacy	Type, consequences, and frequency of short and long-term adverse events following vaccination	Several clinical trials reported a good safety profile of nOPV2. The vaccine was well tolerated among infants, children, and adults.[57]	**Critical**	The GACVS evaluated safety data from Nigeria which vaccinated more than 88 million in the context of outbreak response between March and October 2021documented 6 adverse events of special interest (AESIs) being consistent with a causal association with immunization.[58]
	Risk groups or risk factors for adverse events	Immunocompromised people may be at risk of developing vaccine-associated paralytic poliomyelitis after nOPV2[59]	**Important**	None
	Contraindications	The nOPV2 is contraindicated in those with primary immune deficiency disease or suppressed immune response from medication, leukemia, lymphoma, or generalized malignancy[3]	**Important**	None
	Immunogenicity of nOPV2	Several clinical trials were conducted to evaluate the immunogenicity of nOPV2 among adults, children, and infants. The studies reported nOPV2 protection against poliovirus type 2 comparable with that of OPV2 while	**Critical**	Immunogenicity of nOPV2 was evaluated in outbreak response settings. The assessment reported a seroprevalence

[57]GPEI, Clinical summary for novel oral polio vaccine type 2 (nOPV2)

[58]World Health Organization. (2022). Report from the first joint meeting (virtual) of WHO Global Advisory Committee on Vaccine Safety and WHO Advisory Committee on Safety of Medicinal Products, 14–16 June 2022. Weekly Epidemiological Record, 97(34), 397-407.

[59] WHO (2020). Recommendation for an Emergency Use Listing (EUL) of Novel Oral Polio Vaccine Type 2 (nOPV2)

		being more genetically stable and less likely to be associated with the emergence of type 2 circulating vaccine-derived poliovirus.[60]		of 83% after two doses, evidencing nOPV2 performance on the field.
2. Disease	Epidemiology of Polio and cVDPV2	The annual global burden of paralytic poliomyelitis was estimated to be >350 000 cases in 1988, with WPV transmission reported in more than 125 countries. Polio vaccination campaigns, routine immunization, and surveillance have led to more than a 99% reduction of wild poliovirus cases worldwide while the total number of polio-endemic countries dropped from 24 from 2000 to two in 2022: Afghanistan and Pakistan; and WPV 2 and 3 were globally interrupted. However, VDPV strains continued to circulate in more than 20 countries in the recent years. From 2020 to 2022, 2384 cVDPV2 and 83 of cVDPV1 were isolated from AFP cases while 1314 cVDPV2 and 93 cVDPV1 were detected from environmental samples. Only one case of cVDPV3 was reported from Israel. Out of 657 cVDPV2 events reported in 2022, 74.6% (490 cases) was reported from the African Region, with 50.4% of cases notified from Democratic Republic of the Congo (DRC). In March 2023, Burundi declared an outbreak of cVDPV2 after more than 30 years without polio circulation in the country.	**Critical**	Approximately 90% of cVDPV outbreaks are caused by the type 2 strain of the Sabin vaccine, and this causes a great challenge to polio eradication efforts. These cVDPV2 outbreaks are driven by several factors, most notably declining mucosal immunity to type 2 virus among young children born after the switch; low essential immunization coverage with Inactivated Polio Vaccine (IPV); regional migration patterns that allow the virus to jump from one population to another; delays in detecting cVDPV2.[61]

[60] Macklin, G. R., Peak, C., Eisenhawer, M., Kurji, F., Mach, O., Konz, J., ... & nOPV2 Working Group. (2022). Enabling accelerated vaccine roll-out for public health emergencies of international concern (PHEICs): novel oral polio vaccine type 2 (nOPV2) experience. Vaccine

[61] Cooper, L. V., Bandyopadhyay, A. S., Gumede, N., Mach, O., Mkanda, P., Ndoutabé, M., ... & Blake, I. M. (2022). Risk factors for the spread of vaccine-derived type 2 polioviruses after global withdrawal of trivalent oral poliovirus vaccine and the effects of outbreak responses with monovalent vaccine: a retrospective analysis of surveillance data for 51 countries in Africa. The Lancet Infectious Diseases, 22(2), 284-294.

3. Alternative measures to respond to cVDPV2 outbreaks	Other vaccination strategies	The cessation of tOPV, and the use of monovalent OPV2 (mOPV2) is the only tool to control the transmission of cVDPV2 in affected areas. However, it is evident that the Sabin 2 strains in mOPV2 are genetically unstable, can regain virulence through the reversion of key attenuating mutations, and cause cVDPV2 outbreaks. To reduce the risk, the use of mOPV2 should be large enough to cover populations infected with the outbreak virus, but small enough to avoid unnecessary exposure. Thus, balancing the use of mOPV2 and the requirements to reduce the risk of cVDPV2 is very challenging.[62] The clinical trials and field use of nOPV2 have demonstrated its safety, and effectiveness in protecting against type 2 polio while decreasing the likelihood of cVDPV2 emergence in low immunity settings.[63]	**Critical**	Referring to clinical trial results on the safety and immunogenicity, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization endorsed the use of nOPV2 as the vaccine of choice for response to cVDPV2 outbreaks after the interim recommendation for EUL was issued, and after review of the initial use period is completed and all requirements for use are met.[3]
4. Economic and operational considerations	Direct and indirect costs to procure, store, distribute, and administer the vaccine	The cost of nOPV2 is US$ 0.15 per dose. This means that over the long-term, prices for nOPV2 could approach those for mOPV2. All the storage conditions and requirements as well as storage capacity for vaccine are in place.	**Very important**	The recent cold chain inventory assessment report has evidenced enough capacity for vaccine storage and distribution. No need of additional CCE.

[62] Voorman, A., O'Reilly, K., Lyons, H., Goel, A. K., Touray, K., & Okiror, S. (2021). Real-time prediction model of cVDPV2 outbreaks to aid outbreak response vaccination strategies. Vaccine

[63] Martin, J. (2022). Genetic characterization of novel oral polio vaccine type 2 viruses during initial use phase under emergency use listing—worldwide, March–October 2021. MMWR. Morbidity and Mortality Weekly Report, 71

				GPEI support is available for vaccine supply to the country
	Human, technical, and financial requirements	The nOPV2 are delivered directly into the mouth from the multi-dose vial by dropper or dispenser	**Important**	The vaccine is easier to deliver. HCWs are used to manage such type of vaccines. GPEI support is available for the required human and financial support to deliver the vaccine
	AEFI monitoring and Availability of information systems to measure coverage and vaccine utilization		**Important**	Coverage and vaccine utilization monitoring systems are in place and have been strengthened by introducing digital technologies AEFI surveillance system is in place and has been strengthened for timely detection, investigation, and causality assessment.