POLIO GLOBAL ERADICATION INITIATIVE

TOWARDS POLIO ERADICATION: INSIGHTS FROM THE DEVELOPMENT AND ROLLOUT OF THE NOVEL ORAL POLIO VACCINE nOPV2

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Abbreviations

BMGF	Bill and Melinda Gates Foundation
bOPV	binovalent oral polio vaccine
cVDPV	circulating vaccine-derived polio virus
cVDPV2	circulating vaccine-derived polio virus type 2
EUL	Emergency Use Listing
GACVS	Global Advisory Committee on Vaccine Safety
GPEI	Global Polio Eradication Initiative
GAVI	Gavi, the Vaccine Alliance
IMB	Independent Monitoring Board
IPV	Inactivated polio vaccine
mOPV	monovalent oral polio vaccine
nOPV	novel oral polio vaccine
nOPV2	novel oral polio vaccine type 2
OPV	oral polio vaccine
PDPs	product development partnerships
PHEIC	public health emergency of international con-
cern	
R&D	research and development
SAGE	Strategic Advisory Group of Experts
tOPV	trivalent oral polio vaccine
UNICEF	United Nations Children's Fund
US CDC	US Centers for Disease Control and Prevention
VAPP	vaccine-associated paralytic poliomyelitis
WHA	World Health Assembly
WHO	World Health Organization
WHO AFRO	WHO Regional Office for Africa
WPV	wild poliovirus
WPV2	wild poliovirus type 2

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EXECUTIVE SUMMARY

From the creation of a Consortium to develop a novel oral polio vaccine (nOPV) to the first use of the resulting nOPV2 in the field in 2021 took a period of 10 years – which was remarkably short compared to typical vaccine development times. The history of why and how nOPV2 was created and introduced is important, not only because of the essential contribution nOPV2 is now making towards the goal of eradicating polio, but also because of the opportunities for learning that the process affords. Insights into how the development and rollout of nOPV2 were accomplished reveal much about the realities of contemporary pharmaceutical innovation aimed at achieving a global public good. They provide pointers towards ways in which the speed and effectiveness of product development to tackle an infectious disease can be optimised, as well as indicators of how to strengthen pathways for achieving other global health goals. This combination of insights consequently offers a legacy of learning for the global health community that will be of value long after polio itself has been eradicated.

This study was undertaken through a combination of literature searches and interviews with key actors, which yielded a large database of information to draw upon. Sifting and categorizing the information led to the identification of three main subsets, relating to technology development, global health and organization and governance. The three are not independent, but co-occur and mutually interact throughout the decade-long process of nOPV2 development and rollout. Key experiences, insights and implications in each of these areas form the main components in this report.

The technology development section highlights the contributions of foresight and innovation to the establishment of a virtual pharmaceutical R&D organization that was able to leverage the latest science to develop variants of OPV2 with much less tendency to revert to neurovirulent forms known as a circulating vaccine-derived polio viruses (cVDPVs), and the further innovations used to accelerate product development through the stages of clinical trials and gaining of WHO Emergency Use Listing (EUL) and subsequently WHO Prequalification. The pathway opened is being used to bring forward nOPVs for Types 1 and 3 polio strains and, beyond the polio arena, serves as a model for the development of other global public goods for health.

The global health section illustrates the central importance of the quality of relationships developed as partnerships and collaborations are built and extended in bringing a candidate product through the development, testing and approval stages into field use. Inclusiveness of stakeholders at all levels, effective communications and attention to supply chains are emphasised and will continue to be critical to ensure that the impact of the nOPVs in suppressing occurrence of VDPVs is maximised. Key messages for the wider global health community include the importance of openness to both technological and social innovation in pursuing pathways for rapid response to emerging global health challenges and strengthening global health security; attention to supply capacity and security; and the crucial role of communications.

The organization and governance section traces the critical role that these factors played from the outset in determining the success of the enterprise, and the increasing complexity of the processes involved as the development of nOPV2 moved from early development work to eventual rollout. It highlights the importance and diversity of scrutiny and accountability mechanisms, how these changed along the nOPV2 development pathway and the value of the independent scrutiny and robust assessments of the Independent Monitoring Board as the candidate vaccine moved through EUL approval and into field use. These observations will also be of value in the design of organization and governance structures and processes for other global health initiatives.

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1. INTRODUCTION

CONTEXT

Since the 1960s, vaccines have been used to prevent the disease poliomyelitis caused by strains of the wild poliovirus (WPV). Two types of vaccines are available: an oral polio vaccine (OPV) and an injectable polio vaccine (IPV) (Box 1). In 1988, a resolution of the World Health Assembly (WHA) launched the Global Polio Eradication Initiative (GPEI) with the target of eradicating polio by the year 2000.

Box 1 Polio viruses and vaccines

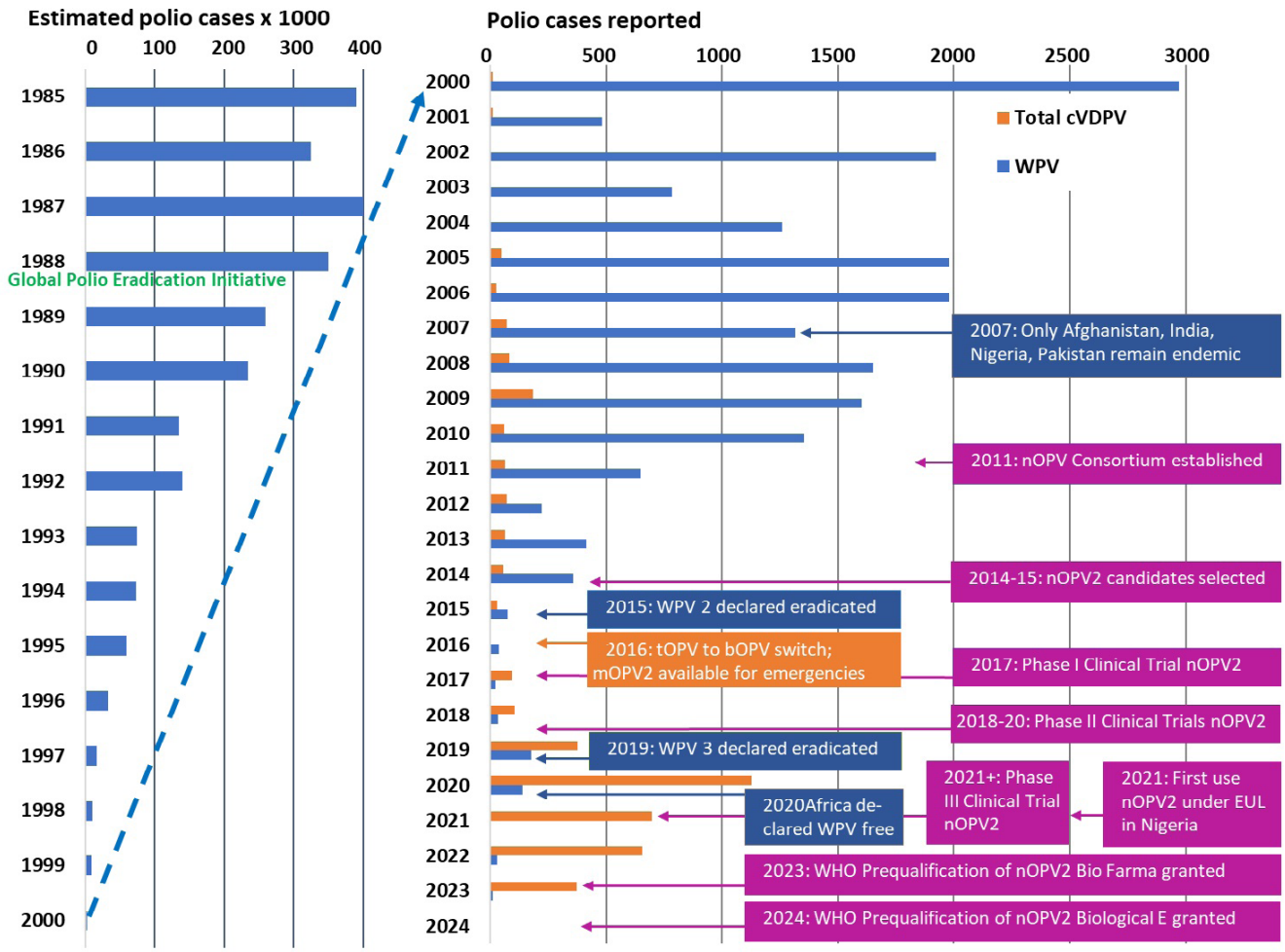
Wild poliovirus (WPV) consists of three serotypes[1] and infection or immunisation with one serotype does not induce immunity against the other two serotypes. Poliovirus type WPV1 has historically been the predominant cause of poliomyelitis worldwide. The trivalent oral polio vaccine (tOPV) used since the 1960s includes attenuated forms of all three serotypes. A single dose of tOPV produces immunity to all three vaccine viruses in approximately 50% of recipients, and three doses produce immunity that is probably lifelong in more than 95% of recipients. Inactivated polio vaccine (IPV) is prepared from the three stains of WPV, which have been fully inactivated, and is administered by parenteral injection. OPV has significant advantages over the alternative IPV.[2-4]

In particular, the live attenuated OPV virus provides better immunity in the gut, where polio replicates, inducing mucosal immunity and limiting poliovirus infection and disease as well as interrupting person-to-person transmission of WPV. The vaccine virus is also excreted in the stool, and in communities with low-quality sanitation it is spread from person to person and helps protect the community. Moreover, OPV is relatively inexpensive and is easier to administer than IPV. Consequently, IPV has been considered more suitable for sustaining immunity in populations already having high levels of protection in geographies where WPV has been eradicated.

However, like other live, attenuated viruses in vaccines,[5] OPV viruses have the capacity to revert to neurovirulence through a variety of mechanisms.6 In the case of OPV, this 'genetic instability' can result in cases of vaccine-associated paralytic poliomyelitis (VAPP) and, in geographies where there is low immunity, to emergence of a circulating vaccine-derived polio virus (cVDPV) that causes clinical symptoms like those seen with WPV. [2,7-10]

A Consortium to develop a new oral polio vaccine with reduced tendency to cause cVDPV was established in 2011, and the first field use of the resulting product to control a polio outbreak in Nigeria took place in 2021. The context in which this achievement occurred, within a notably short period of 10 years (prior to the emergence of COVID-19 in 2019, novel vaccine development from initiation to use in the 21st Century typically required up to 15 years to the end of Phase III testing)11 is summarised in Box 2. This depicts the progress made by the GPEI, the challenging occurrence of cVDPV and major milestones on the pathway to the development and first use of novel Oral Polio Vaccine type 2 (nOPV2).

Box 2 WPV eradication, cVDPV and nOPV2



The history of why and how the new oral polio vaccine was developed and introduced is important, not only because of the essential contribution nOPV2 is now making towards the goal of eradicating polio. It is also significant because the process provides opportunities for learning that are relevant to achieving other global health goals. The experience provides insights into the contemporary realities of product development that aims at achieving a global public good. It demonstrates ways in which the speed and effectiveness of product development to tackle an infectious disease can be optimised, as well as highlighting ways in which other factors, including communications, social and institutional relationships and organizational factors interweave with technology aspects to influence the outcome.

This report details findings and draws lessons from a study undertaken by Hi5 Governance. It highlights many positive results and opportunities to learn from innovative features of the development and rollout of nOPV2. It also details challenges and problems that were encountered during the rollout, some of which have been documented in published literature while others were identified in the frank views and comments expressed during the anonymous interviews, reflecting the opinions of individuals and based on recollections and hindsight.

The global health context in which the lead vaccine candidate for nOPV2 was clinically evaluated, subject to regulatory scrutiny, gained EUL and rolled out was exceptionally complex. Unusual circumstances included (a) the urgency of dealing with a major surge in cVDPV2 which began in 2016 following the global switch from tOPV to bivalent bOPV, accompanied by introduction of Sabin-type monovalent mOPV2 to control any cVDPV2 outbreaks;[12] (b) engagement in the EUL process while it was under development at WHO; and (c) the need to roll out nOPV2 while the world was experiencing the COVID-19 pandemic, which was massively disrupting and stretching health systems, distorting public health priorities, damaging supply chains, limiting access to populations needing vaccination, and polarising attitudes towards vaccination in general as a safe and effective public health measure. This very complex context should be borne in mind in considering the difficulties and deficiencies mentioned.

METHODS

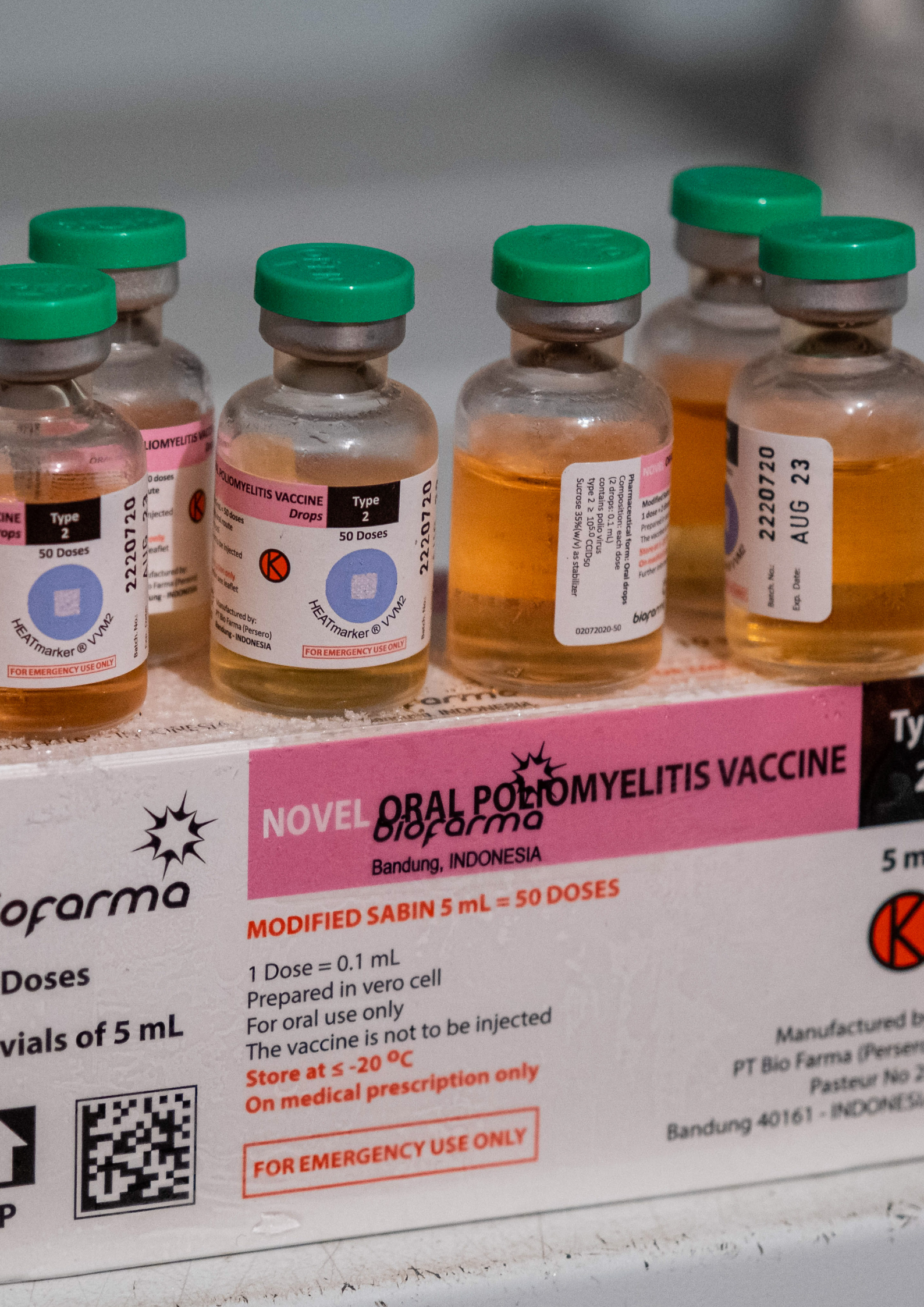
This study was undertaken through a combination of literature searches and interviews with key actors. An internet search identified more than 300 hits related to nOPV2 development and use, with a selection made of about 100 relevant items. Priority was given to: (a) all papers encountered related to nOPV2 development and use that were published in peer-reviewed journals; selected 'grey' publications (documents and web articles) from organizations engaged in the development and use of nOPV2, describing strategies, plans, methods and results; and media reports providing commentaries on processes, challenges and significance, in particular from science-based media outlets and professional organizations.

Sifting and categorizing the information led to the identification of three core aspects, relating to technology development, global health, and organization and governance. The three aspects are not independent, but co-occur and mutually interact throughout the decade-long process of nOPV2 development and rollout. Cross-cutting issues, therefore, emerged as a fourth area to be examined and these are woven into the lessons described throughout the three sections presented in this report.

The issues flagged in a preliminary inspection of the literature were adopted as the starting point for the interview arm of the study. Individuals to be interviewed were identified from a combination of consultations with organizations active in polio eradication, the development of nOPV2 and global health in general. In total, 27 semi-structured interviews were conducted between August and October 2022. All interviews were recorded and collated in a database. Themes and comments were extracted from the interviews to align with the three categories and cross-cutting issues. These are referenced throughout the report in the corresponding sections. Interviews were conducted by telephone and lasted up to 60 minutes. The purpose of the interviews was to:

- consolidate lessons learned from the use of nOPV2 from medical, public health, political, economic perspectives, validating and expanding the previously outlined lessons learned13 and strengthening understanding of drivers and challenges
- understand the documentation needs from key stakeholders that could contribute to providing readily accessible learning of lessons
- filter the understanding of key stakeholders about how nOPV2 is contributing to a public good and bring value for other public health initiatives.

Prepared questions were used as entry points and invited each interviewee to describe their overall role in nOPV2, the time period of their involvement, the processes used, and examples of what had worked well and where challenges and difficulties had been encoutered. Depending on the initial replies, further questions were used to probe and clarify points. Each interviewee was also invited to add anything further they considered relevant to identifying lessons from the development and rollout of nOPV2, as well as any other people they recommended to interview.


POLIOMYELITIS VACCINE
Drops
Type 2
50 Doses
HEATmarker ® VVM2
FOR EMERGENCY USE ONLY
Batch No.: 2220720
Exp. Date: AUG 23
Manufactured by:
PT Bio Farma (Persero)
Bandung - INDONESIA
Pharmaceutical form: Oral drops
Composition: each dose (2 drops: 0.1 mL) contains polio virus type 2 ≥ $10^{5.0}$ $CCID_{50}$
Sucrose 35%(w/v) as stabilizer
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NOVEL ORAL POLIOMYELITIS VACCINE
bioFarma
Bandung, INDONESIA
MODIFIED SABIN 5 mL = 50 DOSES
1 Dose = 0.1 mL
Prepared in vero cell
For oral use only
The vaccine is not to be injected
Store at ≤ -20 °C
On medical prescription only
FOR EMERGENCY USE ONLY
Doses
vials of 5 mL

2. TECHNOLOGY DEVELOPMENT

EXPERIENCES AND INSIGHTS

- nOPV2 development was based on clear evidence of public health need, scientific opportunity and a well-defined pathway to organise and finance a global public good for health.
- The nOPV Consortium, functioning as a virtual pharmaceutical R&D organization, provided a flexible and elastic structure to take forward product innovation and development.
- Engagement of highly qualified experts and partner organizations, adherence to Good Practice guidelines for laboratory, manufacturing and clinical trial stages and detailed scrutiny by ethics committees and regulatory bodies helped build confidence in product safety and efficacy.
- Acceleration processes and designs in product development and clinical trials and the use of the emerging WHO Emergency Use Listing (EUL) all contributed to an unusually rapid progress from initiation of development to first use in the field.
- nOPV2 was designed to greatly reduce the occurrence of genetic reversion of the Type 2 vaccine strain to neurovirulent forms causing poliomyelitis. After two years of field use and around 600 million doses given, the first few cases of cVDPV2 linked to nOPV2 appeared in 2023.

IMPLICATIONS

For polio eradication: A major new tool, nOPV2, is now available to meet the serious challenge of cVDPV. Moreover, nOPV1 and nOPV3 strains are on the pathway to development and clinical use, and their finalization can benefit from the development, production and field experiences gained with nOPV2.

For other global health initiatives: Creation of a global public good for health is facilitated by close attention to science, technology, organizational and finance factors. There are always likely to be unexpected issues arising during the development process and it is therefore important to plan from the outset for constant openness to new science, evidence and opportunities and to pre-design an organizational structure that is sufficiently flexible and elastic to adapt and change with circumstances.

The origins of nOPV2 began with the anticipation of a public health challenge whose solution would require development of a new product – a foresight which very soon proved accurate. Development and rollout required innovation to be embedded in every aspect, from financing and structuring the operation to leveraging the best science available and seeking opportunities to accelerate the pathway from the laboratory to the clinic. Key aspects of this history and insights that can be drawn from it are examined below.

FORESIGHT

The decision to develop a modified version of OPV was informed by important perspectives in three areas, concerned with public health, science and the creation of global public goods for health.

1. A clear public health need was evident

By 2010, the ambition of the GPEI to eradicate polio was significantly off-track (Box 2). The target of global eradication by 2000, set when the GPEI was established in 1988, had been missed,[14] as were subsequent targets.[15] Although there had been a reduction of more than 99% in global cases caused by the wild poliovirus (WPV) from c. 350,000 estimated cases in 1988 to 2971 reported cases in 2000, the subsequent erratic appearance of WPV cases in the following years evidenced continuing challenges in the polio eradication endgame. A WHA resolution in 2008 requested the Director-General of the World Health Organization (WHO) to develop a new strategy to reinvigorate the fight to eradicate polio and also to submit proposals for a mechanism to mitigate the risks of inadvertent reintroduction of poliovirus and re-emergence of polio after interruption of WPV transmission.[16] In a further signal of concern, in 2010, the WHA established an Independent Monitoring Board (IMB), to monitor the implementation and impact of the latest GPEI Strate-

gic Plan (2010-2012) and advise countries and partner agencies on corrective actions as appropriate. The IMB's first Report, in April 2011, cautioned that some countries were still off track and that achievement of the milestone of global cessation of transmission by the end of 2012 was at risk.[17]

While the pace of progress towards polio eradication appeared to be stalling, a long-known, unfortunate feature of the OPV (Box 1) developed by Albert Sabin and first used in 1961 could no longer be ignored. Genetic mutations can occasionally lead to the live, attenuated viruses in OPV reverting to neurovirulence and can result in cVDPV that causes clinical symptoms like those seen with WPV, in geographies where immunity is low. While the incidence of disease due to WPV was declining, cVDPV was being observed in areas of low-vaccine coverage.[18-19] In 2009, there were 1604 reported polio cases caused by WPV and 184 cases caused by cVDPV.

Going forward, key considerations included that (1) the date for achievement of polio eradication remained uncertain;[H 17] (2) even after eradication, the need for polio vaccination would continue for many years to come;[20] and (3) in supporting herd immunity and tackling any sudden outbreaks, live, attenuated oral polio vaccines have important advantages over IPV (Box 1).

Consequently, while the disease burden as such was not very visible to the wider community,[#6] there was a strong public health argument for considering the development of an improved OPV that would not lead to cVDPV cases.

2. Science advances offered insights into cVDPV causes and prevention

Greater knowledge about polio viruses had merged in the 1990s and 2000s. New understanding of RNA viruses led to recognition that most of them have highly mutable genomes that are potentially capable of very rapid evolution and that polioviruses are among the most rapidly evolving of all RNA viruses.[18,21-22] Advances in the use of polymerase chain reaction (PCR) techniques and antigenic methods such as enzyme-linked immunosorbent assay (ELISA) made possible the large-scale screening of polio samples for VDPVs in specimens from patients affected by acute flaccid paralysis, a key symptom of poliomyelitis.[23] Following a cVDPV outbreak in Hispaniola in 2000–2001, the Global Polio Laboratory Network adopted these techniques. They were also applied retrospectively to reveal evidence of cVDPV outbreaks from different OPV strains occurring as far back as the 1960s, with type 2 being prominent. By 2004, the results led to a warningJ that "It is likely that all polio cases will soon be associated with OPV use, causing the risk-benefit ratio for continued OPV use to shift dramatically."

In parallel, the revolution in genetics brought about by advances in capacity to sequence genetic codes rapidly and to relate sequences to functional characteristics was providing a deeper level of understanding of the genetic mutability of the OPV in use since the 1960s to immunise against polio.[24-25] In particular, there was increasing evidence of the occurrence and consequences of point mutations in polio viral RNA that led to reversion to virulence, and growing availability of tools for engineering short stretches of RNA into a viral genome that might be able to greatly reduce the incidence of such reversions.[26]

Consequently, it was evident that the available science now made it possible to rationally design attenuated polioviruses with much greater genetic stability and lower tendency to revert to virulent forms.[27-28]

3. Global public goods for health

Eradication of an infectious disease is an example of achieving a global public good in the health arena. To date, only one infectious disease in human beings (smallpox) has been eradicated, while several efforts to eradicate others have so far failed.[29] Disease eradication efforts generally involve a combination of public health, environmental and pharmaceutical approaches. Of particular importance in the pharmaceutical arena has been the rise, from the 1990s, of product development partnerships (PDPs) supported by public and not-for-profit funders in collaboration with the private sector. PDPs have been successful in bringing a number of new drugs for neglected diseases into clinical use in recent years,[30] but have generally been hampered in scope and slowed in progress by shortfalls and uncertainties in long-term funding, as evidenced in the global R&D analyses reported in 2010-2011.[31-32]

Consequently, there was recognition that the development of an nOPV could be undertaken through a goal-driven collaborative approach and that this would, from the outset, require strong support from public/not-for-profit sources.

nOPV CONSORTIUM

In 2011, a Consortium, supported by the Bill and Melinda Gates Foundation (BMGF) and with PATH as the coordinating partner on R&D, was established with the goal of developing novel OPV (nOPV) strains that would eliminate the problem of cVDPV.[13,27,33] The initial focus of the nOPV Consortium was on type 2 virus, as WPV2 was no longer circulating and the imminent global withdrawal of Sabin type 2 from the trivalent vaccine tOPV and switch to a bivalent vaccine (bOPV) increased the risks of outbreaks of cVDPV2.[34] The type 2 component of tOPV has been responsible for 90% of all cVDPV cases.[35]

Several notable features that were built into the Consortium, which operated as a virtual pharmaceutical R&D organization, would prove to have a decisive impact on the progress and outcomes. Some organizational and financing features of the Consortium are discussed in Section 4, while others are presented below.

The product development process, from inception to first field use, was generally regarded as having been remarkably swift by previous standards. Nonetheless, some interviewees commented on a few areas where they felt that progress was slower than might have been achieved and/or outcomes were less than optimal. Among these, it was commented that PATH's terms of engagement, as the coordinating partner on R&D for the nOPV2 Consortium, were based on time contributed rather than results achieved and that this did not provide a strong incentive for speed or a goal-driven approach.[#27] It was also suggested that there was no clear regulatory pathway planned at the start and that, prior to engagement with the EUL, work on preparations for regulatory approval had not been consistently well managed by the Consortium.

nOPV Consortium as a virtual pharmaceutical R&D organization: The nOPV Consortium took a 'virtual' pharmaceutical R&D approach[36-37] through an international, collaborative framework. Collaboration initially involved researchers at the UK's National Institute for Biological Standards and Controls, the US Centers for Disease Control and Prevention (US CDC), the US Food and Drug Administration, and the University of California at San Francisco. Later, as development moved towards the clinical stages of testing and large-scale production, Batavia Biosciences (Netherlands) and Bio Farma (Indonesia) became involved,[38] bringing expertise in producing vaccines in general and OPV specifically and experience in working with national regulators.[#9] In 2019, an nOPV2 Working Group was created, in which each GPEI partner nominated one person as their core group member. This further strengthened the existing linkages between the nOPV2 Consortium and the GPEI and provided a mechanism to manage and coordinate activities to enable rapid and effective rollout of nOPV2 by GPEI.[39-40] In 2021, the nOPV2 Working Group transitioned to become the nOPV Working Group, to include also a mandate to support the development of nOPV1 and nOPV3 vaccine candidates.[34,41]

Cutting-edge science and innovative strategies: The virtual organization structure enabled the Consortium to engage cutting-edge science,[#26] technology and experience from around the world in all stages.[2,27,41] Novel OPV strains were designed, produced and underwent pre-clinical testing, from which candidates were identified that were at least as attenuated as Sabin type-2 strains, had enhanced genetic stability (reduced potential to revert to a neurovirulent phenotype), and similar antigenicity and immunogenicity.[2,27]

Two of the candidate strains (nOPV2-c1 and nOPV2-c2) were selected to take forward to Phase I and Phase II clinical trials which examined and compared their safety, immunogenicity, shedding and genetic stability.[41] In trials in Belgium, a unique, rapidly-constructed, purpose-built contained environment, Poliopolis, was created[#26] to perform Phase 1 testing of both nOPV2 candidates in healthy adult volunteers.[42-44] As well as the regulatory and technical aspects, psychological support for the volunteers (who were recruited from both Belgium and the Netherlands, requiring inter-governmental collaboration) during the 28-day isolation period was a critical factor in completion of these trials. Subsequently, ‚Vaccinopolis' has been established in Belgium as a permanent facility where vaccine trials requiring a high degree of containment can be conducted – a decision accelerated by COVID-19.[#18] The nOPV2 clinical trials in Belgium and Panama led to selection of the c1 candidate strain for further development,[45] while other countries, including Lithuania, Dominican Republic, Bangladesh, and Gambia, conducted later trials to fill in gaps.[#06]

Regarding the product design strategy, the nOPV Consortium decided to explore a number of different genetic modifications of the Sabin vaccine strains to try to increase genetic stability, suppressing return to neurovirulence while sustaining immunogenicity.[27,41] Several parallel lines of research were established to investigate the effects of different mutations to the poliovirus RNA, including ones that would affect the protein capsid, and criteria established in advance to judge the results. It was commented that the decision about when the different modifications that gave positive outcomes should be combined was taken later than it might have been and this had some negative impacts. Interviewees suggested that the lateness in decision-making resulted from caution on the part of the Scientific Advisory Board commenting on the product development, including reluctance to incorporate the capsid-related modifications. Interviewees considered that, as a result of delays in decision-making, (1) when the pressure to move towards clinical development mounted after major problems with cVDPV2 emerged in 2016 and nOPV2 development was greatly accelerated, there was insufficient time to complete the evaluation of all vaccine candidates in the pipeline and the best possible candidate may have been missed; and (2) with earlier decisions, it would have been possible to move faster to the clinical studies.[#25,#27]

Following the tOPV to bOPV switch in 2016,[#04,46] with a monovalent Sabin OPV2 vaccine (mOPV2) being introduced to deal with any cVDPV2 outbreaks, there was an unexpectedly large increase in cVDPV cases,[47] which became the predominant source of polio globally35 (Box 2). Interviewees expressed views that there was insufficient planning for the possible consequences of the switch from tOPV to bOPV and that the need should have been recognised for a higher level of coverage with inactivated polio vaccine (IPV) to avoid cVDPV2 outbreaks. The need for a novel OPV type 2 became more urgent, and further acceleration in its development was required. Acceleration methods[41] included rapidly mounted control trials before global cessation of Sabin OPV2 use, executing nOPV2 clinical trials in staggered, parallel trials, studying only a high-dose level in participants who had been fully vaccinated against all polio types, empowering a data and safety monitoring board common to all nOPV2 studies, using satellite sites for rapid subject enrolment, and real-time data generation by primary labs to inform trial conduct. Alongside acknowledgement of the innovativeness of these approaches, it was the view of some interviewees that the establishment of clinical trials in Africa and Asia was slow and this was contrasted with the much more rapid and numerous trials conducted in Latin America. This was considered to be related to the differing levels of clinical trials expertise among those responsible for the work in the different regions.[#27]

The continuing international spread of poliovirus had been declared a public health emergency of international concern (PHEIC) in 2014.[48] The Consortium seized the opportunity to engage with WHO to make use of the emerging new WHO Emergency Use Listing (EUL) procedure prior to Prequalification, which aimed to help tackle global health challenges such as PHEICs,[49-51] with the result that, in 2020, nOPV2 was the first product to receive EUL listing.[52] The experience gained in this process is discussed in Section 3 on global health below.

At the rollout stage, a problem with manufacturing capacity and supplies to the field was encountered. Efforts were made to provide supplies of nOPV2 vaccine at the earliest possible time following EUL, including by advance establishment of a manufacturing facility at Bio Farma (Indonesia). However, criticisms were made by interviewees that (1) the demand for nOPV2 was greatly under-estimated; and (2) the reliance on a single manufacturing centre in the early rollout phase created contributed to the initial shortage of sufficient supplies[53] to meet heavy demand when cVDPV2 outbreaks multiplied in 2021.

CONFIDENCE BUILDING IN PRODUCT SAFETY AND EFFICACY

Confidence building for a new product, such as a vaccine, which aims to prevent rather than cure a disease, rests on a combination of factors. These include evidence rooted in science and technology, sound implementation of public health programmes and effective communication with all key stakeholders along the pathway from regulators to recipients.

For the development of nOPV2, confidence concerning the soundness of the underlying science and technology rests in part in its tracking of the well-defined pathway to new drugs and vaccines. This is governed by Good Practice guidelines for laboratory, manufacturing and clinical trial stages and detailed scrutiny by ethics committees and regulatory authorities. However, the accelerated pace, the pressures generated by the urgency of addressing the cVDPV problem and the very closeness of the Consortium to partners intimately engaged in and committed to the goals of the GPEI created the need for extra effort to ensure robustness and transparency in the evidence presented. Moreover, the emergence of the novel polio vaccine in an era when vaccine 'hesitancy' had become a serious challenge in public health programmes globally,[54-55] and the maturing of nOPV2's development to the point of clinical introduction at a time when the public health emergency of the COVID-19 pandemic and controversies over vaccine effectiveness, safety and access were at the forefront of global attention, were added pressures (see Section 3 below). The extra effort required to build confidence in nOPV2 has been manifested in the engagement of the Consortium with regulators – especially in the WHO processes leading to EUL listing and Prequalification – and also in working with GPEI and its partners at global and country levels, as well as with media, to communicate to country programmes and communities the robustness of scientific evidence[#02] for safety, efficacy and public health benefit. Three years after its EUL and with more than 1 billion doses administered, in December 2023 nOPOV2 manufactured by Bio Farma (Indonesia) was granted WHO Prequalification status[53,56] – the first vaccine to employ this route and the only example to date of a global public-private partnership driving vaccine development, production, supply, rollout, and monitoring.[57] WHO prequalification for a second nOPV2 supplier (Biological E. Ltd, India) was granted on 29 July 2024.[58]


PARK BILAL GUNJ LHR
THE FALCON SCHOOL SYSTEM

3. GLOBAL HEALTH

EXPERIENCES AND INSIGHTS

- nOPV2 development was rooted in a commitment to innovation as one of the keys to success. It identified and made use of a number of critical leverage points with the potential to create a large change that can transform the outcomes in a complex system. They included recognition of the opportunity to create more genetically stable OPV strains with greatly reduced tendency to undergo reversion leading to cVDPVs, and decisions to adopt a virtual pharmaceutical organization model, to form the nOPV2 Working Group and to seek an accelerated route to implementation of nOPV2 via the emerging WHO EUL process.
- As an initiative requiring multiple collaborations and partnerships, the success of nOPV2 development and rollout depended heavily on the quality of the relationships built among diverse stakeholders at all levels, from global to national and local. Attention to inclusiveness, effective communication and confidence-building with different audiences were all of central importance.
- Supply chain and data management and programme monitoring were also critical components of the nOPV2 rollout. Flexibility became essential when supply shortages, in the face of expanding cVDPV outbreaks and under the constraints of COVID-19 disruptions and lockdowns, became a factor in meeting higher-than-expected demand. This highlighted the need to have more than one manufacturer involved.
- Effective, speedy communication was vital for planning for product acceptance and uptake, countering misinformation, and raising awareness and confidence in the vaccine. The polio eradication partnership recognized the importance of engaging with communities and addressing concerns and misconceptions to ensure successful vaccination campaigns. Nevertheless, there were some difficulties experienced in this regard when cVDPV2 outbreaks increased and some countries preferred to wait for nOPV2 supplies rather than use the available mOPV2.

IMPLICATIONS

For polio eradication: The granting of an EUL to nOPV2 provided a game-changing tool and is expected to be followed by rapid advance of nOPV1 and nOPV3 candidates through development and into field use. The extent to which their deployment will meet the objective of enabling cVDPVs to be suppressed and poliomyelitis to be eradicated will depend on the effectiveness of production and supply systems and the comprehensiveness of local immunization coverage, supported by effective communication campaigns and engagement with local stakeholders.

For other global health initiatives: Openness to innovation, in both technological and social dimensions, is one of the keys to success. Innovations that shorten the time taken to establish worldwide access to new products can greatly increase their impact on global health. The EUL process pioneered by nOPV2, very shortly afterwards followed by EUL for the first COVID-19 vaccine, opens a new pathway for rapid response to emerging global health challenges and can help to strengthen global health security.

As well as contributing to the global health goal of eradication of a specific infectious disease, the development and implementation of the nOPV2 vaccine affords experience and insights relevant to other global health areas, along a spectrum that includes innovation in product development and regulation, organization of global health partnerships, managing information, communication and outreach and responding to global health emergencies.[#09,#11] Learning related to nOPV2 that is relevant both to polio eradication and the wider global health agenda is described below. As several interviewees[#02,#03,#16] in this study noted, collaboration is critical and „the clinical development and the science are very important, but perhaps what is even more important is the ability to create and develop partnerships and to work with different stakeholders successfully."[#16]

OPENNESS TO INNOVATION

Attempts at disease eradication have usually started with the premise that sufficient knowledge and experience were at hand, and that tools (e.g., for prevention, diagnosis, treatment) already available, appropriately applied in public health programmes and backed by strong social and political commitment, would suffice to ensure success, with no further product innovation being necessary.[59-61] However, to date, only one infectious disease in human beings (smallpox) has ever been declared eradicated[62] (1980), and rinderpest, a viral disease in cattle and other animals, was declared eradicated[63] in 2011, with both successes having depended on vaccines. Attempts at eradicating many other infectious diseases have so far failed. Reasons have included problems with the technical tools (e.g., lack of an effective vaccine, pesticide and drug toxicity, development of drug and pesticide resistance, recognition of pathogen reservoirs, weaknesses in surveillance), as well as with public health, political and economic aspects.[15,64-68] A further factor in some cases has been the emergence of new knowledge that has deepened understanding of the disease and revealed new challenges. Lessons that can be drawn from this history include that a disease eradication programme needs to constantly seek to identify or anticipate emerging challenges and to draw on innovation to develop solutions, and that flexibility and capacity to adapt are critical to success in the face of setbacks and shocks.

The history of nOPV2 illustrates and adds depth to this evolving appreciation of the factors contributing to the advancement of a disease eradication programme. Key aspects are described here.

Leverage points - Seeking to acquire and leverage greater knowledge about the disease during the eradication programme: Having taken account of advances in knowledge in virology and genetics since the GPEI was initiated, the nOPV Consortium was constructed on the principle of co-opting cutting-edge science to solve the problem presented by the recognition of cVDPV as a significant challenge to completion of eradication. The assessment that there was potential to develop a genetically more stable generation of nOPV vaccines (see Technology Development section above), rather than abandon OPV in favour of IPV, can be seen as an example of systems thinking to identify a critical 'leverage point' – an action with the potential to create a large change that transforms the outcomes in a complex system.[69] Additional leverage points included decisions to adopt a virtual pharmaceutical organization model, to form the nOPV2 Working Group and to seek an accelerated route to implementation of nOPV2 through the emerging WHO EUL process, which are all discussed below. Innovations that shorten the time taken to establish worldwide access to new products can greatly increase their impact on global health.[#09]

Applying 'integrated innovation' to a global health challenge: Recognition that innovation has social as well as technological aspects that can help to maximize the potential of its impact on global health,[70] and that business innovation should also be included, was the focus of a 2010 Grand Challenges Canada paper.[71] This defined 'integrated innovation' as the coordinated application of scientific/technological, social and business innovation to develop solutions to complex challenges. The development of point-of-care diagnostics,[72] on which Grand Challenges Canada partnered a 2009 request-for-proposals from the BMGF, was cited as a case study. The concept of integrated innovation is clearly reflected in the BMGF's design of the nOPV2 Consortium launched in 2011. The technologically innovative solution of developing a new OPV was accompanied by social and business innovations in the construction and financing of the Consortium's 'virtual pharmaceutical organization' elastic model and in the subsequent clinical testing, regulation under EUL and rollout through the GPEI via the nOPV2 Working Group. At each stage, the research, development and governance models were developed, adjusted and extended to adapt to evolving circumstances, meet challenges and take advantage of opportunities.

Creating global public goods for health: It is increasingly recognized that creating global public goods for health[73] requires intensive cooperation, sustained championing and robust, long-term financing[74] – points that were further highlighted during the COVID-19 pandemic. [75] While the opportunity exists for establishing a multilateral process for global public goods for health,[76-77] in the absence of an implemented platform it has been left to a few interested actors to try to fill the gap (see section on Technical Development). Along with the products brought into use by a number of PDPs, the success achieved in the development and rollout of nOPV2 is another important demonstration of what is possible and serves to encourage renewed efforts to fill the gaps in global health.[#12] One of the important aspects of the development of nOPV2 was ensuring effective, early communication and dialogue with regulators at both global and local levels and

consistent messaging to Bio Farma Indonesia.[#08,#11] It will be important that the lessons learned from this experience are shared in accessible forms for those who have not encountered polio in many years.[#04,#10]

LEARNING ON THE BENEFITS AND CHALLENGES OF THE EUL

As the first product to receive WHO Emergency Use Listing (13 November 2020), nOPV2 has provided valuable experience for other products to draw upon.[#16] The EUL was itself an innovation launched by WHO in 2020 to replace the earlier Emergency Use Assessment and Listing (EUAL) procedure, which was used during the West Africa Ebola outbreak of 2014-2016 but which had not led to listing for any submitted Ebola vaccine candidates.[78] The nOPV2 experience covers not only the process of gaining EUL status but also how to manage the implications that flow during subsequent product rollout.

Gaining EUL listing: The EUL is designed as an accelerated procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics in order to expedite their availability in the course of a public health emergency. It is, therefore, intended to function in contexts where testing is not yet fully completed to the point where normal WHO Prequalification[79] would be possible, but a rigorous risk-based assessment is required, relying on the available data on quality, safety, efficacy and performance. PATH's experience in product development helped support the process, which was complicated, among other aspects, by the fact that the manufacturer, Bio Farma, was not the sponsor of the clinical trials and also that access to the EUL's reviewers went through the EUL's secretariat, rather than being direct.[#14] An important criterion for success, beyond the efficacy of the product itself, is the capacity to ensure a high-quality outbreak response.

Significant features of the process of gaining EUL for nOPV2 included:

- **Engagement:** The nOPV2 developers engaged strongly with the WHO's EUL-associated machinery[#04,#08] (the WHO's Prequalification Team had been assigned the role of EUL Secretariat).[78] WHO and nOPV2 project partners already met in November 2018 to discuss possible approaches to pre-licensure use of nOPV2 and listing under the EUL procedure which itself was still under development at that time. They interacted with the WHO Strategic Advisory Group of Experts on Immunisation (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS), both of which endorsed the application for listing.[49] The roadmap[50] towards an EUL for nOPV2 provided further details of the process and the requirements the developers would need to meet, both regarding data required for assessment of the application and, if successful, subsequent monitoring of the performance of the vaccine deployed to countries.
- **Process acceleration:** The urgency of the public health emergency for which an EUL is granted adds pressure for essential data to be acquired with maximum possible speed. As part of its accelerated approach, the nOPV2 Consortium clinical trials generated multiple incremental interim trial reports to enable rolling submission and review for EUL, and major scale-up and optimization of laboratory capacity to generate data for EUL submission (see also Section 2 under nOPV Consortium, for further examples of acceleration strategies).[F 41] Nevertheless, it was suggested by some interviewees that the 12-month timeframe for the EUL process had been excessively long and that shorter timelines could have been possible, leading to earlier field use.[#06,#27]
- **Communications:** The roadmap[50] also required development, ahead of the submission, of a communication strategy to facilitate the emergency use.[#19] There was extensive dialogue with countries where nOPV2 might be deployed,[#11] as well as sharing of a detailed vaccine manufacturer's dossier, to explain the EUL and the potential risks and benefits of the novel vaccine. As an indicator of the success of this approach, more than a dozen countries approved the use of nOPV2 within the first year of the EUL.[#02,#05,#07]
- **Vaccine deployment readiness:** To be verified for nOPV2 use under the EUL, countries needed to meet requirements across seven areas, covering coordination, approvals (regulatory and national decision-making), cold chain and vaccine management, surveillance, safety, advocacy, communications and social mobilization, and laboratories.[80] In December 2020, GPEI instituted a process for nOPV2 Readiness Verification and Dose Release and provided interim guidance for the Initial Use Phase.[81]

Rollout under EUL: Following the EUL,[41,52] by January 2024 1 billion doses of nOPV2 had been administered across 35 countries globally since its first use in Nigeria in March 2021.[56] Challenges encountered during this period that provide valuable experience for other global health initiatives include:

- Limitations in nOPV2 supplies[53] constrained full rollout after EUL and the mounting of prompt response campaigns when cVDPV outbreaks occurred.[82-83]
- Some countries experiencing cVDPV outbreaks in the 2020-2021 period delayed implementing full vaccination responses until they could obtain nOPV2 supplies, resulting in many polio cases that could have been prevented using available mOPV2.[#05,84]
- In March 2023, the first seven cases of cVDPV2 linked to nOPV2 use were reported, as well as environmental samples, stemming from two separate and new emergencies occurring in Burundi and the Democratic Republic of the Congo. This required effort by the nOPV2 Working Group,[85] GPEI[86] and WHO[87] to manage expectations in communications about the relative safety and stability of the new vaccine (which are viewed as very successful)[#05] and the public health advantages of polio vaccination.

The EUL process has itself learned from the early experience with nOPV2 and is evolving to suit newly emerging circumstances, for example, by requiring applicants in a number of programs to present at least some Phase 3 clinical trial data.[#22] However, one interviewee noted that, at the time the first EUL's were in preparation, there was surprisingly little outreach from the COVID-19 communications team to the nOPV2 team.[#05]

Subsequently, an analysis[88] of the nOPV2 EUL experience offered observations on key lessons learned to aid accelerated development of and greater global access to further safe, effective, quality COVID-19 vaccines. These included, in the regulatory area, emphasis on establishing platforms for collaborations between the WHO, the subject matter experts, the national regulatory agencies with special expertise and, where appropriate, the national regulatory agencies where the products will be used, to align as early as possible on the content and the format of the regulatory submission. Clinical studies should be accelerated as much as possible to shorten the timeline to EUL. In parallel, the chemical manufacturing strategy needs to focus on planning to manufacture at the scale required to address the pandemic while adhering to the struct guidelines for Good Manufacturing Practice. The importance of secure funding for the high-risk stages of scale-up, manufacturing and supply were highlighted, as well as the economics of subsequent use. Post-deployment, ongoing safety monitoring was emphasised, both as an essential need for partient safety and as a critical input to the evential gaining of WHO Prequalification or full licensure by another regulatory authority.

Prequalification: On 27 December 2023, nOPV2 recevied WHO's first-ever prequalification approval for a vaccine being used under its EUL regulatory pathway.[57] Based on rigorous assessments of quality, safety and efficacy data from completed clinical trials, information provided by Bio Farma Indonesia and the granting of full licensure from the Indonesian regulatory authority, Badan POM, the allocation of WHO Prequalification status will help to streamline and accelerate regulatory approval for nOPV2 use in countries that need it. nOPV2 has thus demonstrated the viability of the EUL-Prequalification pathway as a route to providing vaccines.[56]

COLLABORATION AND CONSULTATION

Building on a well-established platform for polio eradication and bringing in new partners: The clinical development and deployment of nOPV2, initiated through pre-clinical stages by the nOPV Consortium, was further pursued in collaboration with the existing, well-established GPEI platform. In its work since 1988 towards the eradication of polio, the GPEI has developed an extensive infrastructure and network of partners to support this effort. This platform provided the opportunity to bring in new partners and stakeholders to collaborate around a common goal and high-priority issue.89 The nOPV Consortium-GPEI collaboration aimed to ensure that the vaccine was clinically developed and deployed efficiently and effectively. Efforts were made to bring relevant stakeholders at global, regional and national levels in the process,[90] with wider networks of multiple stakeholders able to support the development and rollout of nOPV2.[#11] However, some involved were of the view that there was not always enough actual listening to some voices.[#04,#19]

The core nOPV2 Working Group was established to include representatives from all six GPEI partner agencies (Rotary International, UNICEF, BMGF, GAVI, US Centers for Disease Control and Prevention, and WHO). To advance work in key technical areas, specific sub-groups that include membership from experts beyond GPEI were established at different times, covering research, data analysis and modelling; initial use country support; manufacturer support (including regulatory support); genetic characterisation; safety; and nOPV2 Working Group liaisons for vaccine supply, communications and readiness verification.[39,41] The collaboration also facilitated important engagements with WHO Prequalification machinery and Executive Board and WHA reporting and decision-making processes.[#04]

nOPV2 thus exemplifies how flexibly building on and adaptng platforms and engaging a wide range of stakeholders can contribute towards successful outcomes in global health.[91] It was stressed by several interviewees[#05,#11,#19] that, by collaboration around a common goal and high-priority issue, the global health community can achieve significant progress in disease control and elimination.

Anticipated and effective communication: Effective, speedy communication[#13] has been crucial for planning for product acceptance and uptake,[#19] countering misinformation, and raising awareness and confidence in the vaccine.[92-93] The polio eradication partnership recognized the importance of engaging with communities and addressing concerns and misconceptions to ensure successful vaccination campaigns.[94] Prior to the deployment of nOPV2, communication efforts focused on educating stakeholders and communities about the benefits of polio vaccines and dispelling any misinformation or myths that may have existed.95 This aimed to build trust and acceptance of the vaccine, increasing the likelihood of successful uptake and implementation. Digital social mobilization means, such as social media, were also used to raise awareness and confidence in the vaccine.[#21] This approach allowed for targeted communication and engagement with different forms of media,[#23] communities and stakeholders, helping to address any concerns or misconceptions in real-time although there were also incidences of social media spreading rumours and misinformation that had to be countered.[#05,#20]

Overall, consultation with country stakeholders by the GPEI and partners was an important factor in moving the nOPV2 rollout process forward and helped to ensure that the vaccination campaigns were tailored to the specific needs and cultural context of the communities being served.[96-97] This built greater trust and acceptance of the vaccine[#05] and its importance in protecting children from polio. Successful strategies included identification of a focal point in each country to provide an anchor for communications and involving a broad team from the start to create an appropriate mindset.[#23] Some countries established a specific task force to drive the process.[#23] UNICEF and WHO regional offices were key in this process through their respective procurement and communications support.[#21] By involving country stakeholders in the development and implementation of vaccination campaigns, the global health community can enable responsiveness to the local context and needs. This approach contributes to the success of vaccination campaigns and can be applied to other global health initiatives to improve the effectiveness and sustainability of interventions.

Nonetheless, there were particular communication challenges encountered that related to cVDPVs and nOPV2. The handling of communications relating to cVDPVs was considered very delicate within the GPEI. Interviews uncovered examples of this sensitivity:

- The GPEI seemed reluctant to acknowledge the severity of the threat posed by cVDPV, which related to a fundamental weakness in the genetic stability of Sabin OPV and therefore in the key tool on which the polio eradication programme as a whole depended. This reluctance was reflected in a preference for stressing the importance of vaccine coverage rather than directly addressing cVDPVs as a key issue. For example, one of the interviewees commented: "The challenge with polio isn't technical. It's not like we're missing a magic tool that we need to eradicate polio. And nOPV2 is not the magic tool that will eradicate polio. What it takes to eradicate polio, truthfully, is access and political will. If we have access to all the areas and the political will to mount, high quality, rapid responses polio would be gone. (...) I think this is the lesson for eradication initiatives, that no tool will fix the problem." Another interviewee emphasised the importance of high-quality campaigns to achieve high levels of overall vaccine coverage in order to eliminate outbreaks.[#01]
- There were concerns that fear of developing vaccine-related cases of polio could weaken the acceptance of vaccination and impair the eradication efforts. This became increasingly problematic after the 2016 switchover, when cVDPV2 cases began to greatly outnumber WPV cases. The arrival of nOPV2 therefore needed to be framed in a way that would encourage its uptake without creating alarm about the overall eradication programme. Several sources suggested that this was not well handled and there was not always internal and external coherence in messaging.[#15,#26] Some interviews commented that communications during rollout were initially not always particularly well prepared and had to be developed on an ongoing basis to prevent misinformation from spreading.[#20,#21] To facilitate successful campaigns, informed decision-making at country level was vital and one interviewee was of the view that more could have been done, including by undertaking face-to-face briefings in countries.[#03] Another interviewee considered that the communications group within GPEI was very externally focused and not really focused on internal communications to get everyone within the programme aligned.[#11]

Of particular relevance was the decision by WHO AFRO and some of its member countries not to use mOPV2 to try to curtail cVDPV2 outbreaks, but instead to wait for the arrival of nOPV2,[#05,#11,#19] supplies of which were inadequate to meet demand in the initial rollout in 2021. Commentaries highlighted several problematic areas, including:

- Overall expectations for nOPV2 needed to be better managed.[98] There were tensions and failures in communication between headquarters and regional and country levels about the downside of delaying action on cVDPV2 outbreaks, as a result of which the outbreaks were larger than they might have been. It was suggested that communication efforts had not been sufficiently clear[#11] to counter any misunderstanding that nOPV2 could not give rise to cVDPV2, while in reality cases of cVDPV2 derived from nOPV2 have been observed, but at a much lower rate than would have occurred with mOPV2.[99] Some interviewees spoke about the continuing need for vigilance to address concerns about the safety, efficacy and genetic stability of nOPV2.[#03,#05,#26]
- There was confusion/lack of clarity in communication among members of the GPEI and inconsistencies in approach at country levels, resulting in insufficient buy-in to accepting the risk assessment modelling, with fears that immediate use of mOPV2 would be less good than waiting for nOPV2, leading to lack of policy coherence between the global, regional and country levels on a key strategic issue in outbreak control;[#01,#19]
- There was insufficient attention by GPEI to the voices of actors at regional level.#04 One interviewe[#19] commented that, after the EUL in late 2020, it was unofficially being said that WHO AFRO would not want to use mOPV2, but there was a lack of desire to address this at the global level, leading to divergent views and policies. This included divergences between WHO Geneva and WHO AFRO on the use of mOPV2, as well as between WHO and UNICEF on the involvement of global figures in public communications at the regional and country levels. Another interviewee[#26] commented that rollout could have been more measured with a clear emphasis on continuing to use existing vaccines in some cases.

A key lesson learned from nOPV2 rollout regarding initial communications to countries was that timely, simple, streamlined communication and high-level advocacy are necessary, as well as repeated messaging that countries could absorb when it was relevant for them.[#11] Initial confusion around guidance for nOPV2 versus mOPV2,[#19] at a time when supplies of nOPV2 were very constrained, did not help countries in making appropriate decisions,[#15] while there was also a political factor in the selection of countries for rollout.[#05,#19,#25]

ENGAGEMENT AT COUNTRY LEVEL

The risks of not fully eradicating polio remain high, with consequences for the global community as a whole and for individual countries.[100-107] All WHO regions have reported at least one cVDPV outbreak since 2000, highlighting that maintaining surveillance for poliomyelitis and for environmental samples of polioviruses after local elimination is essential.[108-110] Technical guidance documents and general advice for country implementation are critical elements for managing this process and for steering rollout of nOPV2 in appropriate ways.[111-115] However, in addition to this, a number of engagement processes, particularly at country level, have also been essential elements for success, including the following:

Extensive consultative processes with country stakeholders: As seen in the GPEI's long experience in the polio eradication effort, involvement of local communities and stakeholders in the planning and implementation of vaccination campaigns is essential. S 85 This requires understanding the different contexts[#20] and levels of risk in each country and adapting the global recommendations and approach to local campaigns.[96,116] In the rollout of nOPV2, simple, streamlined communication and high-level advocacy were necessary. WHO and UNICEF, in particular, played strong roles in facilitating such communication and dialogue at multiple levels#02,[#03,#05,#11,#21] and often used personal contacts and relations to speed up the process. However, there were occasional tensions between global and regional actors with disagreement on modelling predictions and timing of use of nOPV2 versus mOPV2 partly due to a lack of coherence across all stakeholders.[#05,#08,#11,#26]

Informed decision-making at country level: Ongoing communications during rollout were initially not always particularly well prepared and had to be developed on an continuing basis to prevent misinformation from spreading and facilitate successful campaigns.[#20#21] Tools and protocols were developed over time, which helped to combat misinformation and streamline the process for countries. To ensure that countries had the information they needed to make informed decisions about the use of the vaccine, an innovative new mechanism was developed to share information dossiers. These dossiers contained comprehensive information on the safety and efficacy of the vaccine, as well as data from clinical trials and other studies. They were developed through a collaborative process involving global health organizations, vaccine manufacturers, and regulatory agencies. They provided a transparent and evidence-based approach to decision-making, allowing countries to make informed decisions about the use of the vaccine based on the latest scientific evidence. This was a critical step in building support for the use of nOPV2 and enabling the verification process. Several interviewees[#02,#03,#21] confirmed that, alongside extensive face-to-face dialogue and consultation, especially with Ministries of Health, this process helped to build trust and confidence in the vaccine, aming to provided a clear and transparent process for evaluating the safety and efficacy of the vaccine.[117-118]

Developing local capacity and resources for rapid deployment and greater self-sufficiency: A key benefit of building local capacity in the context of polio eradication is the ability to rapidly deploy vaccines and other health interventions in response to outbreaks or other emergencies. Various mechanisms were put in place to support this process and speed up the readiness verification process. These included inviting high-risk countries to workshops to raise awareness; formal and informal engagement with countries; training of partners in advocacy, communication and social mobilization; supporting countries with consultants to meet human resources gaps; reducing the number of requirements for authorisation to release from stockpiles; and timing the communications with countries only when they had an outbreak and were more responsive.[#11,#21] It was also important that countries had funds available for local campaigns in the weeks preceding local rollout.[#20] A dashboard was established to track progress in readiness verification. However, a challenge was faced in some countries that were slower to roll out nOPV2 as they had not had to deal with outbreaks for some years.[#25,#21]

By building local capacity and involving local stakeholders, such as religious leaders and local authorities,[#20] countries can more quickly and effectively respond to public health crises, helping to limit the spread of disease and reduce the impact of outbreaks. Acknowledging and strengthening the role of women was also noted to be an important factor that was neglected in some countries and making sure that there were no major gaps in coverage resulting in large groups of vulnerable children.[#21,#26] In addition, building local capacity can help to reduce reliance on external partners and resources, which will be important for sustaining polio eradication efforts over the long term and, more broadly, for strengthening capacities to respond to other disease challenges and future public health emergencies. Building local capacity also has the potential to create new economic opportunities and improve public health outcomes more broadly. By investing in local health systems and infrastructure, countries can improve access to healthcare services and support the development of local industries and businesses, creating new jobs and improving economic outcomes.

ADAPTING TO THE COVID-19 PANDEMIC

The outbreak of COVID-19, a respiratory disease caused by the coronavirus SARS-CoV-2 which was first reported in China in late 2019, was declared by the WHO Director General to constitute a PHEIC[119] on 30 January 2020 and characterized as a pandemic[120] on 11 March 2020. The rapid spread of this pandemic resulted in major loss of life and put intense pressure on health services around the world. Responses included major restrictions in personal contact and movement, interruptions to work and disruption to supply chains. Many vaccination campaigns, including those for polio eradication, were suspended.[121]

These challenges came as the polio eradication programme was facing severe challenges due to increasing cases of cVDPV and while nOPV2 was still navigating the pathway to EUL. On 13 November 2020, nOPV2 became the first product to receive EUL, to be followed six weeks later by the first COVID-19 vaccine (Pfizer/BioNTech) on 31 December 2020 and during 2021 by several other COVID-19 vaccines.[122]

Recognizing that, to place the GPEI back on the path to eradication, it was necessary to adjust to the new realities, including among other changes, to operate with an emergency tempo, in 2021 the GPEI issued a new Global Polio Eradication Strategy 2022-2026 to supersede the Polio Strategy 2019-2023. The new Strategy took account of new tools and approaches, including nOPV2, and the need to address vaccine-derived polioviruses more concertedly, as well as new operations tactics in light of the ongoing COVID-19 pandemic, with particular emphasis on integrated approaches.[89]

Adapting to the disruptive global context: For nOPV2, the process of scale-up and manufacturing was underway as the COVID-19 pandemic emerged and accelerated, and there was significant disruption to operations, facilities and people.[#04] This necessitated a flexible and adaptive approach to laboratory operations, work schedules and protection mechanisms, development of alternative supply chains, and learning to work with the constrained capacities of the country regulators.[#02,#08,#09,#17,#25] The rollout of nOPV2 also occurred during the COVID-19 pandemic, causi ng substantial cross-effects. While these resulted in significant additional challenges for the early use of nOPV2, as discussed below, they also present an opportunity for learning.[123-124] In a context of global shut-down and reprioritization of scarce resources, adapting to the disruptive global context was essential for both managing the COVID-19 crisis and limiting the rise of cVDPV.[125] his involved careful planning and collaborating with the nOPV2 vaccine manufacturers and distributors to ensure that vaccine supplies were available despite the disruptions caused by the pandemic,[#08] negotiating with countries when there were shortages,[#04] and sometimes joint efforts[126] for the administration of nOPV2 and COVID-19 vaccines. A further aspect of the disruption caused by COVID-19 was the slowing of clinical trials for nOPV1 and nOPV3 candidates.[#14]

Effective communication again proved crucial in managing the spread of cVDPV in the context of the COVID-19 crisis and limiting the damage.[127] Strong and timely communications efforts were needed[#05,#13] to counteract suspicion, misinformation and vaccine hesitancy.[94,128-129] This involved engaging with communities to promote the importance of vaccination and dispel myths and misinformation surrounding the vaccine at a time when there was growing vaccine hesitancy and concern about the extremely rapid development of COVID-19 vaccines.[#20#23] It also involved providing accurate and timely information to healthcare providers and other stakeholders to support effective vaccination campaigns. Success is evident as most countries with cVDPV outbreaks have been able to control these with two rounds of nOPV2 administration.

When countries were not successful (e.g. Nigeria and Niger), this was due to insufficient reach of vaccination campaigns rather than ineffective vaccine.[#05]

The global health community also leveraged their experiences in managing the COVID-19 pandemic to support the rollout of nOPV2. This included developing innovative strategies for vaccination campaigns, such as mobile vaccination teams and drive-through vaccination centres, that could be adapted to the unique challenges posed by the pandemic. This experience highlights the importance of flexibility and adaptability in global health initiatives, particularly in the face of unexpected disruptions or crises. A key lesson highlighted by several interviewees was the need for a very locally contextualized response as the COVID-19 pandemic affected countries in different ways and at different times. Understanding this against the emergence of cVDPV at varying rates across countries simultaneously battling with COVID-19 required bespoke responses agreed in collaboration with national authorities.[#02]

Managing supply needs: Forecasting and managing supply needs was a crucial aspect in the rollout of nOPV2. Challenges included a slowdown in production due to lack of raw materials, worker absenteeism, and lockdown restrictions; difficulties in mobilizing the vaccine to countries due to lack of cargo services, flights and airport closures; delays in rolling out training and ongoing clinical trials; and competing priorities for the WHO Pre-Qualification team. Shortages in supplies, partly due to the unpredictable extent of cVDPV2 outbreaks, were exacerbated by the massive scale of COVID-19 vaccine production at the time when nOPV2 production was being scaled up after both received EULs.[#02,#08,#09] Addressing these considerable obstacles involved multi-channel communication with countries, flexible procurement models, expanding the number of providers of raw materials,[#08] and adaptive manufacturing processes, all of which were complicated by the contextual challenges of COVID-19.[#09] Multi-channel communication with countries was important for forecasting supply needs, as it allowed for effective collaboration and planning between vaccine manufacturers, distributors, and national health authorities. Flexible procurement models and adaptive manufacturing processes were also noted to be important[130-131] to allow for rapid adjustments to vaccine orders and production schedules based on changes in demand[#25] or other factors. Having initially only one global nOPV2 supplier, Bio Farma in Indonesia, had created a risk to consistent supply[#06,#08,#26] and plans were made to have a second manufacturer supplying nOPV2 in 2024.[85] One interviewee commented that the relatively confined nature of the nOPV2 collaboration compared to that in the COVID-19 response proved to be more effective and less chaotic.[#04]

Another important aspect of managing supply needs was acceptance of EUL as a viable pathway for vaccines and other products. This approach allows for the rapid deployment of vaccines and other products in emergency situations, helping to address critical public health needs in a timely and effective manner. The process of obtaining EUL that was led by the polio eradication community preceded the rapid acceptance of COVID-19 vaccines, and has opened the way for others to follow, helping establish that EUL is now a viable pathway, not just for vaccines but also for other products. Nevertheless, challenges remain with individual country regulatory processes, therefore, ongoing dialogue is likely to be required to ensure that lessons learned are widely shared and remaining concerns are addressed.


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4. ORGANIZATION AND GOVERNANCE

EXPERIENCES AND INSIGHTS

- Initial development of candidate nOPVs was managed through the creation of a virtual R&D organization, the nOPV Consortium, structured as a lead-organization-governed, goal-directed network. This created the framework for a flexible, elastic structure, which proved well suited to the need to bring in the partners and expertise necessary to capitalise on cutting-edge science.
- The commitment by the BMGF at the outset to finance the process through to clinical use was a critically important factor that removed funding uncertainties that might have delayed decisions. It also enabled a shift in the balancing of financial risks against clinical urgency.
- The organization and governance processes though which nOPV2 was developed, tested and brought into use changed substantially over time, moving from the relatively simple lead-organization-governed, goal-directed network to a much more complex one. Establishment of the nOPV2 Working Group together with the GPEI (itself a network administrative organization for a structurally complex network) brought nOPV2 directly into the arena of those who would be engaged in the rollout of the vaccine as part of the overall polio eradication effort. In doing so, it exposed nOPV2 to a large and multi-level array of management and oversight groups with different scrutiny and accountability mechanisms and powers. There was not always complete clarity on the division of roles and responsibilities of actors within this complex matrix.
- Importantly, the nOPV2 Working Group came within the purview of the IMB, which has played a key role in monitoring the progress of the GPEI and has been robust in its analysis and criticism where there have been weaknesses in the Initiative. The IMB lost no time in drawing attention to uncertainties and risks in plans for the rollout of nOPV2 and the contributions it can make towards elimination of cVDPV and the overall goal of polio eradication.

IMPLICATIONS

For polio eradication: The entry of nOPV variants into field use has the potential to have major impact on the suppression of cVDPVs and on progress towards the overall goal of polio eradication. It will be of key importance to ensure that the complex governance structures and the responsiveness of the program to monitoring and feedback and to local situations and setbacks are all able to operate in ways that achieve this potential.

For other global health initiatives: Structure and governance designs play critically important roles in achieving global health objectives. In the creation of a global public good for health, such as a vaccine or drug, the virtual R&D organization provides one working model for product development, as exemplified by nOPV2. The potential for success is greatly boosted by (1) secure, long-term funding; (2) a structural framework that is flexible and elastic; and (3) accountability mechanisms that ensure a focused, goal-driven effort, but one that is responsive to new evidence and emerging challenges and opportunities. The need for new skills and resource capacities as the product advances towards clinical use in the field implies the expansion of collaborations and partnerships to bring in many other stakeholders, and with it, a major expansion in the complexity of governance, monitoring and accountability channels operating.

As well as the technical achievement of creating a new oral polio vaccine with enhanced genetic stability132 and the global health impact of this innovation in the effort to eradicate polio, unique features of the organization and governance processes through which nOPV2 was developed, tested and brought into use also offer important opportunities for learning. The insights, discussed below, can be of benefit both in the end stages of polio eradication itself and in global health more broadly.

CONCEPTUALIZING THE APPROACH TO DEVELOPMENT OF A GLOBAL PUBLIC GOOD FOR HEALTH

In efforts to create global public goods for health, such as vaccines and drugs (see also Section 2: Technology Development, under Foresight), a major challenge has always been in securing funds for global public goods. In general, control and eradication programmes for infectious diseases have, like the GPEI, been financed by a combination of funds from public (e.g. international agencies and governments) and not-for-profit (e.g. foundations) sources, sometimes with an existing drug being donated by a pharmaceutical company.[133] In cases where weak commercial incentive results in 'market failure', financing the development of new pharmaceuticals has been a particular problem.[134-136] It has usually been left to the public and not-for-profit sectors to undertake the development of effective, affordable and accessible drugs and vaccines as global public goods for health, in particular through the mechanism of product development partnerships.[137-138]

While the BMGF had been extensively involved in supporting PDPs for a number of years, direct engagement in the development of a pharmaceutical product marked a new step.[#27] Operating as a virtual pharmaceutical R&D organization, the nOPV2 Consortium drew on the evolving landscape of drug development for infectious diseases,[138] and in particular, the growing understanding of the roles, advantages and limitations of PDPs,[32] in taking up and adapting the concept of a 'virtual' pharmaceutical R&D approach.[36,139] This created the framework for a flexible, elastic structure,[34] which evolved as a global partnership that included scientists, vaccinologists, immunologists, laboratory experts, clinical researchers and vaccine manufacturers (see also Section 2: Technology Development, under nOPV Consortium).

FINANCING DEVELOPMENT OF nOPV2

Experience had shown that the success of PDPs, while substantial, had generally been restricted by shortfalls and uncertainties in long-term funding. This was evidenced in the global R&D analyses[31-32] reported in 2010-2011 when the nOPV2 Consortium was being launched.

A critical factor in the timely development of nOPV products was the commitment by the BMGF at the outset to finance the process through to clinical use.[#04,#12,#26] This removed funding uncertainties that might have delayed decisions, with science driving the decision-making,[#25] although it potentially excluded further consideration of other options.[#04] It also enabled a shift in the balancing of financial risks against clinical urgency.[#06,#25] For example, when the cVDPV2 situation worsened in 2019, calculated risk-taking led to the decision to move forward with at-scale production of nOPV2 while the product was still under evaluation. Using an early investment model, a number of vaccine producers in different countries were examined, both for technical capacity and the regulatory environment.[#24] PT Bio Farma, Indonesia was selected as the first producer and contracted to establish manufacturing of up to 200 million doses of nOPV2 by the end of 2020, aiming to ensure availability immediately after an EUL was granted. A bigger challenge may arise with ongoing funding to complete the rollout of nOPV2 where needed so that the final goal of eradication is achieved[#05] as countries have received the vaccine free of charge.[#08]

EVOLVING GOVERNANCE

To date, there has been little analysis published concerning the organizational structures and governance processes involved in the development and rollout of nOPV2. However, study of these provides a rich source of experience and insights to inform future global health initiatives. These illustrate the increasingly complex governance processes and structures involved as the nOPV2 project evolved through successive stages of research, development, clinical testing, regulatory assessment and field use. They highlight how engagements between different sets of actors with different mandates and responsibilities move the project forward, while also illuminating how decision-making and accountability operate in multi-partner settings.

Network governance: This is a process by which collective action is achieved through interconnected institutions that may span government, business and civil society. Its relevance to global health initiatives and networks has been examined[140-142] and the nature of the GPEI, as an example in which it serves as a network administrative organization for a structurally complex network, has been discussed.[143] It was

noted that the complexity of the model had advantages in enabling efficient operation to be balanced with inclusive decision-making and the sustaining of both internal and external legitimacy, as well as balancing flexibility with stability. However, there were also challenges noted in the model, including that the network governance structure can have the effect of blurring lines of accountability and responsibility. Some GPEI members themselves have acknowledged the complexity of its organizational structure as presenting challenges, including in coordination, communication and management of expectations, as well as in the management of multi-level relationships among headquarters, regional and country-level components in relation to nOPV2, with the importance of highly effective leadership emphasized.[#05,#15,#16,#25]

The nOPV2 project began in 2011 with the creation of the nOPV Consortium (see Section 2: Technology Development), which can be viewed as having the BMGF as the hub of a lead-organization-governed, goal-directed network.[144] This variant involves one member organization taking the lead in convening members and managing the network, while others take on specialized core roles.[145] It drew on a number of the advantages of network governance, including capacities for alignment, consensus building, and priority-setting, enabling a wide range of skills, experience and views to be brought together[#04,#10,#12,#25] while also benefitting from the stronger guiding opportunity afforded by the lead organization role, including in ensuring effective overall direction and speedy decision-making and delivery of flexible funding.[#18] The lead role also conferred the opportunity to provide an institutional framework, manage complex processes especially with regulators, and play strategic and diplomatic roles with countries. This structure proved well suited to the focused task of bringing a novel product through the successive stages of design, research, development and clinical trials, having strong expertise in incubation of novel products (PATH) within the core Consortium[#14] while enabling new collaborators and expertise to be brought into the Consortium as required. This included through people employed directly by BMGF (e.g., in the case of an expert in manufacturing, process development and scale-up) as well as through external links (e.g., in the establishment of an innovative 'Poliopolis' clinical trial virus containment facility in Belgium or to conduct essential control trials with OPV in Panama to provide historical baseline data with mOPV2 before the global withdrawal of type 2-containing OPV in May 2016, while nOPV2 was still under preclinical development).[#06,#09,#10] The consortium also coopted outside experts to provide independent views at critical stages (e.g. in the design of candidate vaccines and the assessment of evidence regarding selection of the candidate vaccine to take forward into final clinical development).[#14,#25]

The complexity of the structure, as well as willingness of the participant organizations to share confidential information and to accept risks in a shared, diffuse way in order to move forward, were among the challenges that needed to be managed to keep the process progressing.[#14] Among its roles, PATH coordinated the filling of gaps that appeared during the R&D process, as well as providing continuing regulatory and clinical support through to and beyond the EUL stage. Another aspect of management pertinent to the organizational model was that, while clinical development involved a sequence of organizations, a common data safety monitoring board was established to provide independent oversight with continuity over the whole development process.[#14,#27]

It is notable that no large industry partner was involved in the Consortium's R&D work, and it can be argued that some of the process and decision-making would have benefitted from their experience of product development.[#06]

Beyond the R&D stages, the Consortium became a more informal grouping of collaborators led by BMGF, with PATH continuing to play a key role.[#06,#14] As the emerging candidate nOPV2 moved towards the regulatory stage and readiness for rollout, it became necessary to interface more formally with the GPEI, which would provide the channel for vaccine delivery where needed. The Consortium interconnected with the GPEI through the creation in 2019, of the nOPV2 Working Group, which provided coordination and management of all the puzzle pieces[#22] and began to establish a series of sub-groups to advance specific areas of work (see Section 3. Global Health: Collaboration and Consultation). The nOPV2 Working Group interacted extensively with WHO, also a GPEI partner and the host agency for the GPEI, which operates through WHO administrative structures at HQ, regional and country levels.

In 2021, the nOPV2 Working Group broadened its remit to include nOPV1 and nOPV3 vaccine development as the nOPV Working Group. It is interesting to note that, for the development of these new products, the Consortium mode of working is not being replicated. With the opportunity to use the pathways laid by

nOPV2, a collaborative development structured agreement between PATH and the manufacturer, with clear roles and responsibilities for each, provides the basis of the approach.[#14]

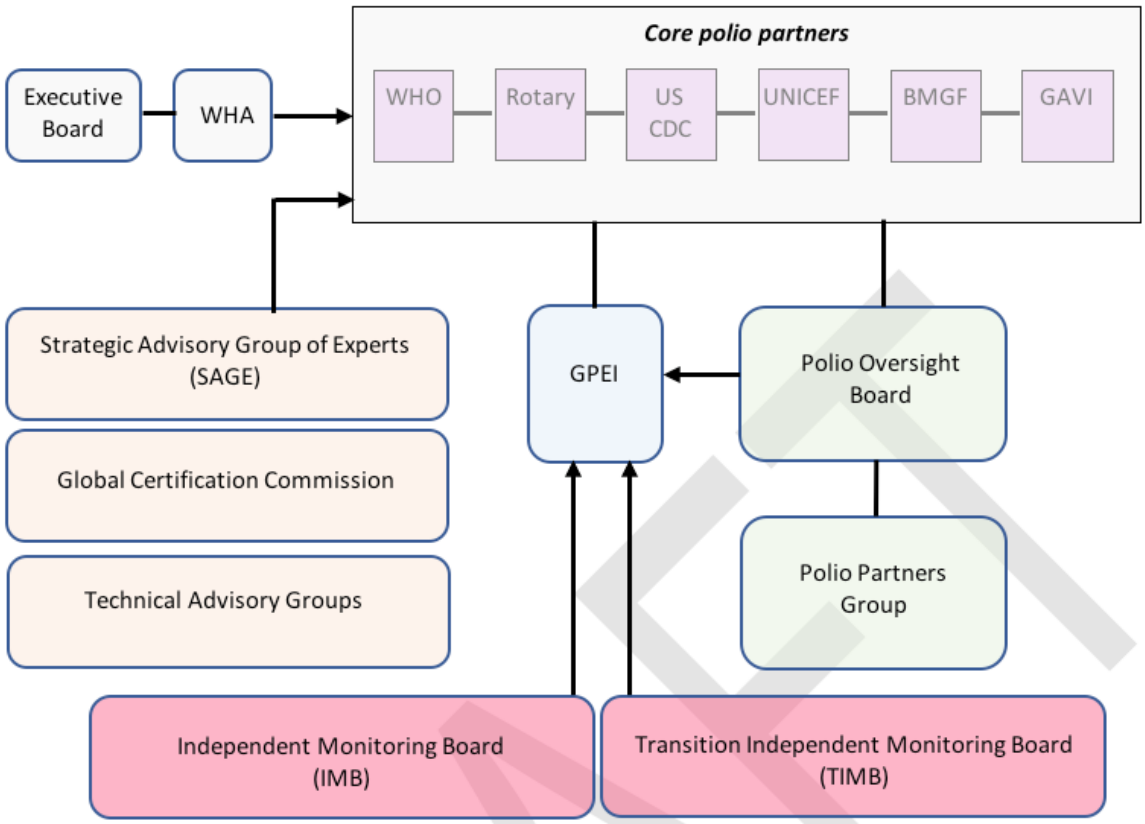
In terms of lessons learned from the overall model of development of nOPV2, the complexity of the governance structures that evolved against a background of changing external contexts sometimes led to a perception of 'chaos'. One interviewee closely involved commented,[#06] "It was good enough to get us the vaccine for public health use. It wasn't perfect. But, you know, sometimes, as we all know, perfection would be a bit of a problem. And so I think if I look back, as chaotic as it was, (...) we got the vaccine for public health uses." On the other hand, another key stakeholder commented that rollout could have been more measured with a clear emphasis on continuing to use existing vaccines in some cases.[#26]

Once the organizational locus moved from the Consortium to the nOPV2 Working Group,[#01] the development and roll-out processes became subject to the complex structures and relationships involved in the GPEI partnership. As highlighted in the section on Global Health, this gave rise to a number of difficulties, especially related to divisions of responsibility and divergent approaches, both along the intra-organizational (e.g., between headquarters/regional/country levels within WHO) and inter-organizational (e.g. WHO-UNICEF) axes. One interviewee referred to the importance of having clear roles and divisions of responsibility, while another spoke about the need to recognise that country partners know their own local context better,[#02,#04] while a third stressed the headquarters view that there should be consistent policy positioning accord across the polio partnership. In the early roll-out period when nOPV2 was in short supply, headquarters took the view, based on modelling, that high quality, response should be as quick as possible with the first available vaccine, to stop outbreaks, while at the regional/country levels in Africa there was a firm belief that the stability of the vaccine outweighs the speed of response and it was better to wait for nOPV2 supplies to be available, and "the partnership hasn't been able to get alignment on that issue".[#01]

Monitoring, evaluation and accountability: Through the course of nOPV2 development and rollout, the changing nature of the governance and collaboration groupings involved also had implications for the nature of the processes of scrutiny to which it was subjected. These processes became increasingly diverse and complex, as did the governance model itself. Several stages can be recognised:

I. Preclinical product development: In the initial, lead-organization-governed stage, responsibility for monitoring, evaluation and accountability of the nOPV Consortium rested ultimately with the network leader and funder, BMGF, to which PATH, as the coordinating partner on R&D, reported.
II. With the advance of candidate nOPV2 vaccines into clinical testing, an additional track of scrutiny was added, which concerned the success of technical development. Following approval by local ethics committees for trials to be held, this involved the globally established process of evaluating candidates for possible clinical use through well-defined stages of Phase I-III Clinical Trials, with detailed examination of evidence by experts and ultimate decision by a regulatory authority. In the case of nOPV2, the urgency of dealing with the growing cVDPV outbreaks resulted in gaining the first-ever EUL to be granted by WHO, rather than a conventional approach to a regulatory body such as the US Food and Drug Administration or European Medicines Agency.
III. The formation of the nOPV2 Working Group as a collaboration between the nOPV Consortium and the GPEI, added new, multiple tracks of scrutiny, many of which were also concerned with how effectively the product development and rollout were being driven and managed and the extent to which the overall goal of polio eradication was being reached. Through the Working Group, nOPV2 was brought into the complex machinery of the network governance structure in which GPEI acts as the network administrative organization. As depicted previously (Box 3),[143] the GPEI Secretariat is hosted at WHO, which was one of the five core polio partners at the time when the nOPV2 Working Group was formed (Gavi, the Vaccine Alliance, known as GAVI, became the sixth GPEI core partner in 2019). Through WHO, the GPEI connects to the reporting and decision-making processes of the Executive Board and of the World Health Assembly, which create the polio eradication initiative. It is also under the scrutiny of the Polio Oversight Board and a broader, more diffuse Polio Partners Group of multiple stakeholders. Key activities are scrutinised and advice given by SAGE, Global Certification Commission and Technical Advisory Groups. The nOPV2 sub-committee of GACVS met every six months to review data on nOPV2's field performance as the rollout progressed, with this enhanced monitoring providing assurance of safety.85 Ongoing safety monitoring is considered by several interviewees as a key remaining challenge although there have not been any major concerns reported to date and genetic stability is being carefully monitored.[#03,#26]

Box 3: Elements and relationships in the GPEI network governance model



It is of particular note that the work of the nOPV Consortium had not been subject to any scrutiny or comment by the IMB during the preclinical development and early clinical trial phases. This changed with the formation of the nOPV2 Working Group and the advancing plans for EUL listing and rollout. The direct linkage with the GPEI and the deepening concern that the IMB had been expressing about cVDPV brought the later stages of nOPV2 development squarely within the IMB's sights. The IMB's 17th Report[146] in 2019 was explicit in stating that the Polio Endgame Strategy 2019-2023 was already failing badly in the objective required by the 2019 WHA, to stop all cVDPV outbreaks within 120 days of detection and eliminate the risk of emergence of future VDPVs. The Report noted that GPEI's new strategy was to move as rapidly as possible to using nOPV2 and that one of the two candidate vaccines would now be brought forward rapidly for EUL. It raised many questions, including about how the candidate selection for final vaccine development would be made, how adequate supplies would be achieved and how available supplies would be allocated, how much confidence there was that the modified virus will not revert to become pathogenic in continued circulation in large numbers, and what were the implications for the development of new monovalent Types 1 and 3 oral polio vaccines. The IMB expressed concern that the GPEI did not seem to have an alternative plan and urged the need for critical thinking to challenge the status quo. By the time its 18th Report[125] was published in 2020, the IMB was discussing "the vaccine-derived polio crisis", with multiple outbreaks in several regions and a five-fold increase in cVDPV cases compared to the same stage in the previous year, attributed to a combination of emergency issuances of mOPV2 and COVID-related cessation of polio field activities. This, and subsequent IMB Reports,[147-149] have continued to highlight challenges, shortcomings and missed opportunities in the rollout of nOPV2, as well as anticipating potential future problems.

CROSSUTTING ISSUES

It was emphasised in the Introduction that the three core aspects on which this report concentrates, relating to technology development, global health, and organization and governance, are not independent of each other. Rather, they co-occur and mutually interact throughout the process of nOPV2 development and rollout. A specific example of this that illustrates interlinkages between the three core areas and reveals a number of lessons of broad significance is the experience of rollout of nOPV2 in Africa, shortly after the novel vaccine gained EUL to combat outbreaks of cVDPV2 (Box 4).

Box 4 JOINING THE DOTS: ROLLOUT OF nOPV2 IN AFRICA

The first use of nOPV2 was in Africa in 2021, in a context made complex by historical, technical, operational and programmatic dimensions. The African region was declared free of endemic WPV in August 2020. However, a variety of factors led to increasing cases of cVDPV2, with over half the global total of more than 1000 cases in 2020 coming from this one region.[150-152] Contributing issues included declining gut immunity in young children to the type 2 virus after countries switched from trivalent to bivalent OPV for routine immunization in 2016; impacts of COVID-19 on the eradication programme; insufficient routine immunization coverage and interrupted and incomplete immunization campaigns; low quality and delayed polio outbreak response; limited resources; and difficulties of access in some places where there were conflicts. All these had resulted in lowering population immunity,[153-155] with 26 countries in the African region reporting cVDPV2 outbreaks in 2020.[156-157]

Following the authorization in November 2020 for nOPV2 to be used under EUL, two factors limited the opportunity for countries to begin using this new tool immediately to control cVDPV2 outbreaks – one being the requirement for each country to meet detailed readiness criteria before nOPV2 could be administered, while the other was the initially limited availability of supplies of nOPV2 from the sole manufacturer, Bio Farma, which proved insufficient in the face of an initial demand that was much larger than had been anticipated. The policy set at the global level while the rollout of nOPV2 was being operationalised was that countries should use the available mOPV2 to control cVDPV2 outbreaks and not wait for nOPV2. This advice was based on modelling, which had shown that, even with its greater tendency to lead to cVDPV2 outbreaks, overall there would be far fewer cases of cVDPV2 resulting from immediate use of mOPV2 when an outbreak was detected than from waiting for use approval and supplies of nOPV2.

However, some countries in the African region, as well as the WHO AFRO regional office, preferred to wait for nOPV2 to become available. According to several interviewees,[#05,#11,#19] there was insufficient buy-in to accepting the risk assessment modelling, with fears that immediate use of mOPV2 would be less good than waiting for nOPV2, leading to lack of policy coherence between the global, regional and country levels on a key strategic issue in outbreak control. One factor in the failure of messaging referred to by interviewees was that there was some reluctance within GPEI to be too explicit about the cVDPV2 risks inherent in using OPVs. There was a perception that it was important to maintain confidence in mOPV2 and also to be cautious about 'over-selling' nOPV2 immediately after its EUL and before it had received regular licensing, as a result of which communications about cVDPV2 had lacked clarity. Another factor cited was reluctance to tackle the historic problem of lack of coherence that arises between WHO's global, regional and local levels. One interviewee[#19] commented that, after the EUL in late 2020, it was unofficially being said that WHO AFRO would not want to use mOPV2, but there was a lack of desire to address this at the global level, leading to divergent views and policies, including between WHO and UNICEF as well as between Geneva and WHO AFRO, on the nature of involvement of global actors at the regional level.

Subsequent assessments indicate that the modelling was correct and that there were more cases of polio as a result of the delays in immunization13 and the need for longer and costlier immunization campaigns to end the outbreaks. As well as lessons for the GPEI itself regarding the need to improve communications and coherence between global, regional and country levels and between partners within the GPEI, there are wider lessons for disease eradication and global health security. These include the need for frankness in explaining issues of effectiveness and risk of approaches, the importance of both the robustness of modelling and of ensuring that there is buy-in of the modelling by key actors; and the need to take account of tendencies for independent approaches by actors at global, regional and local levels – and especially when such tendencies may be accentuated within complex network governance structures in disease control or eradication programmes, resulting in lack of policy coherence.

5. CONCLUSIONS

KEY MESSAGES

This report discusses the development and success of nOPV2, the first new polio vaccine since Albert Sabin's oral polio vaccines in 1960. Notably, nOPV2 has transitioned from WHO's Emergency Use Listing to Prequalification after demonstrating its safety and effectiveness. It addresses challenges posed by the type 2 variant poliovirus and surpasses other vaccines, particularly mOPV2, in safety. The global polio eradication programme strategically developed nOPV2 by prioritizing public health value and leveraging innovations in vaccine science. Collaboration with diverse experts, global partners, and country stakeholders was crucial. Adaptability in the face of mounting outbreaks of cVDPV2 and the COVID-19 crisis, effective communication, and proactive investment in manufacturing were integral to nOPV2's success. The nOPV2 Working Group, with experts in various domains, played a pivotal role in decision-making, regulatory engagement and rollout planning. Involving Ministers of Health and WHO Member States increased their support for the product. The BMGF contributed significantly to nOPV2's success by providing foresight, drive and consistent funding and through fostering goal-driven collaboration.

Implications for polio eradication:
The introduction of the new tool, nOPV2, is a significant development in addressing the challenge of cVDPV. Additionally, progress is being made[158] in the development of nOPV1 and nOPV3, with the experiences gained from nOPV2 contributing to their finalization. The granting of EUL to nOPV2, followed by WHO Prequalification, is seen as a game-changer, and it is anticipated that nOPV1 and nOPV3 candidates will quickly follow suit for field use.

The success of deploying these vaccines to suppress cVDPVs and thereby strengthen the pathway to achieve polio eradication hinges on the efficiency of production and supply systems, as well as the comprehensive coverage of local immunization, supported by effective communication campaigns and engagement with local stakeholders. To fully realize this potential, it is crucial to ensure that governance structures are effective, responsive to monitoring and feedback, and adaptable to local situations and setbacks.

Implications for other global health initiatives:
Creating a global public good for health, such as a vaccine, requires careful consideration of science, technology, organization, and finance factors. Unforeseen issues during development necessitate a proactive approach, emphasizing constant attention to new science and evidence. Planning for flexibility in organizational structures is crucial to adapt to changing circumstances. Success relies on openness to innovation, both technologically and socially, to expedite global access to new products. Pioneering processes like the EUL, as seen with nOPV2 and subsequently with the first COVID-19 vaccine, offer a rapid response pathway to emerging global health challenges, enhancing global health security. Structure and governance designs are pivotal in achieving global health objectives. The virtual R&D organization, exemplified by nOPV2, serves as a model for product development. Success is augmented by secure funding, flexible frameworks, and accountability mechanisms that balance focused, goal-driven efforts with responsiveness to new evidence and challenges. As products advance to clinical use, collaboration expansion necessitates development of intricate governance, monitoring, and accountability channels.

LIST OF INTERVIEWEES

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Nasir Ateeq	UNICEF
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Ilse de Coster	University of Antwerp
Pierre van Damme	University of Antwerp
Martin Eisenhawer	WHO
Edward Fox	Global Health Strategies
Salah Haithami	WHO
Shahin Huseynov	WHO
Harish Iyer	Bill & Melinda Gates Foundation
John Konz	PATH
Ian Lewis	UNICEF
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Joe Swan	WHO
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Amy Weiner	Bill & Melinda Gates Foundation
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Simona Zipursky	WHO / Co-Chair nOPV2 WG

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