IMPROVED VACCINES: NOVEL ORAL POLIO VACCINE

Workshop 5: New and Improved Vaccines on the horizon
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Dr. Ananda S. Bandyopadhyay
Senior Program Officer - Polio

OUTLINE

- *Global polio epidemiology*
- *Novel OPV type-2 (nOPV2): clinical development, manufacturing, regulatory and roll-out strategies*
- *Looking forward*

POLIO: *MANY* DISEASES?

Wild

- Type 1 (highest **case-infection** ratio, **spreads** rapidly)
- Type 2 (***eradicated***)
- Type 3 (***eradicated***)

OPV related

VAPP

- Overall risk in developing countries: 1 case per 4 – 5 million OPV doses.

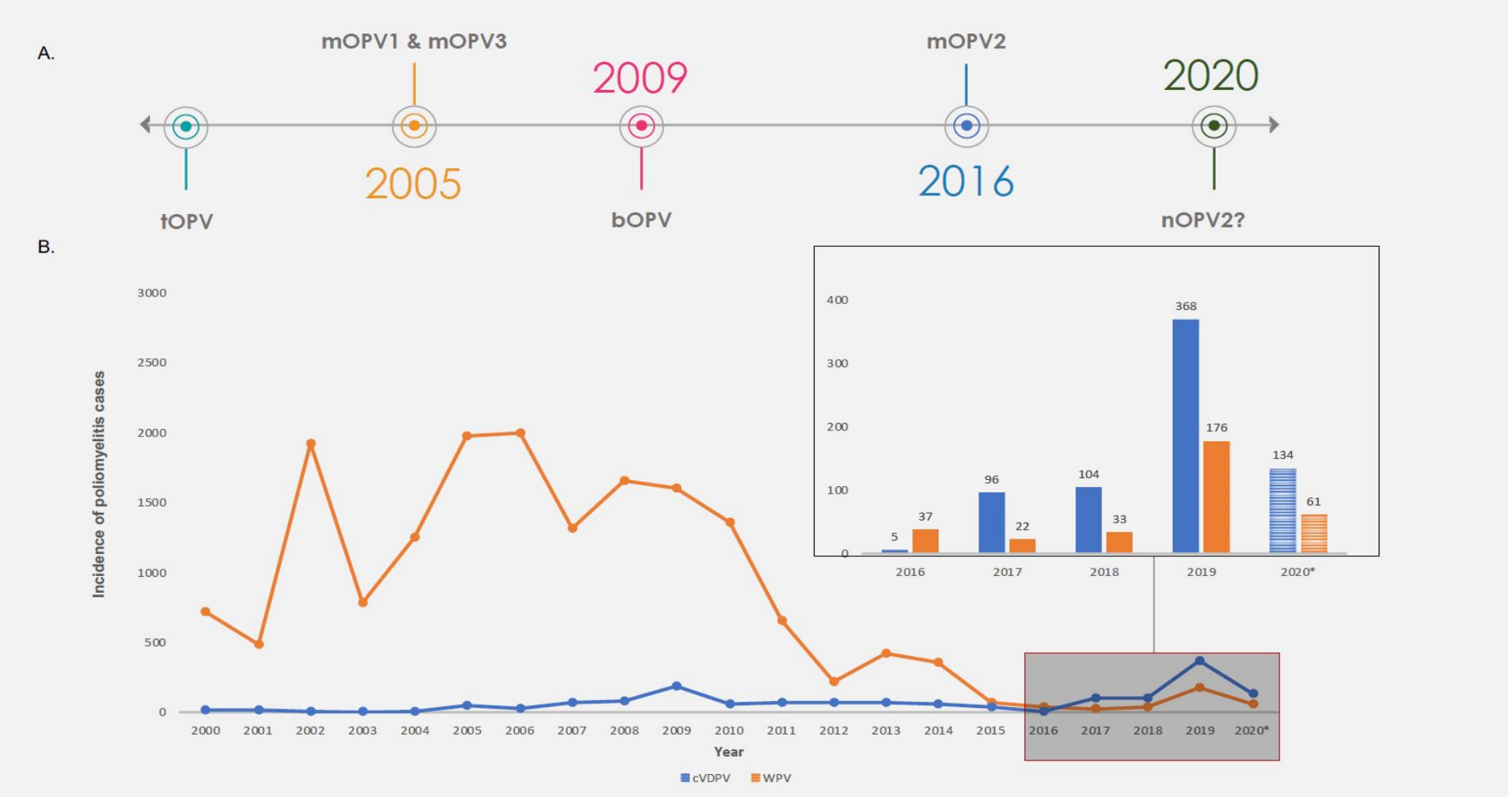
VDPVs

- Most are circulating type 2 VDPVs (cVDPVs)

Adapted from a slide from Walt Orenstein, Emory

GLOBAL INCIDENCE OF POLIOMYELITIS (2000 – 2020*)

Bandyopadhyay, Ananda S.; Macklin, Grace R. Final frontiers of the polio eradication endgame, Current Opinion in Infectious Diseases: 2020



*2020 data incomplete, through June 2020.

GPEI Strategy for Interruption of cVDPV2, 2020-2021

Accelerating the development of nOPV2 is one component of **the GPEI's comprehensive new strategy to stop the spread of cVDPV2,** characterized by improved outbreak response and attention to challenging contexts.

Optimize outbreak response using mOPV2, currently the best available tool for combatting type 2 vaccine-derived polio

Accelerate development of a new vaccine—novel OPV2 (nOPV2)—as a potential alternative for cVDPV2 outbreak response and ultimately as a replacement for mOPV2

Strengthen routine immunization and mitigate cVDPV risk by leveraging GPEI technical staff & synergizing efforts to strengthen immunization delivery systems in high-risk areas

Ensure sufficient supply of OPV2 is available to reach every at-risk child, utilizing innovative strategies as needed

nOPV2: An Innovative Tool to Stop cVDPV2 Outbreaks

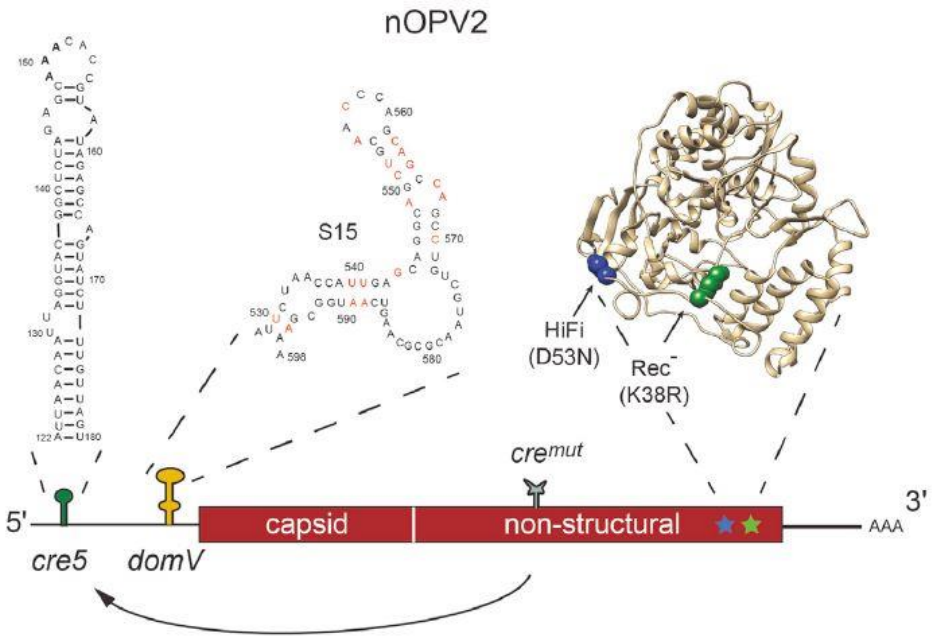
Addresses cVDPV2

The novel oral polio vaccine type 2 (nOPV2) is a new tool developed to better address the risk of type 2 circulating vaccine-derived poliovirus (cVDPV2).

Modification of Sabin mOPV2

nOPV2 is a modification of the existing type 2 monovalent OPV (mOPV2) that clinical trials have shown provides comparable immunity against poliovirus while being more genetically stable and less likely to revert to a form that can cause paralysis. **The increased genetic stability means there is a reduced risk of seeding new cVDPV2 outbreaks compared to the existing mOPV2.**

nOPV2 Genome with modifications



Ming Te Yeh, Erika Bujaki, Patrick T. Dolan, Matthew Smith, Rahnuma Wahid, John Konz, Amy J. Weiner, Ananda S. Bandyopadhyay, Pierre Van Damme, Ilse De Coster, Hilde Revets Andrew Macadam, and Raul Andino. Engineering the Live-Attenuated Polio Vaccine to Prevent Reversion to Virulence. Cell Host and Microbe. 2020.

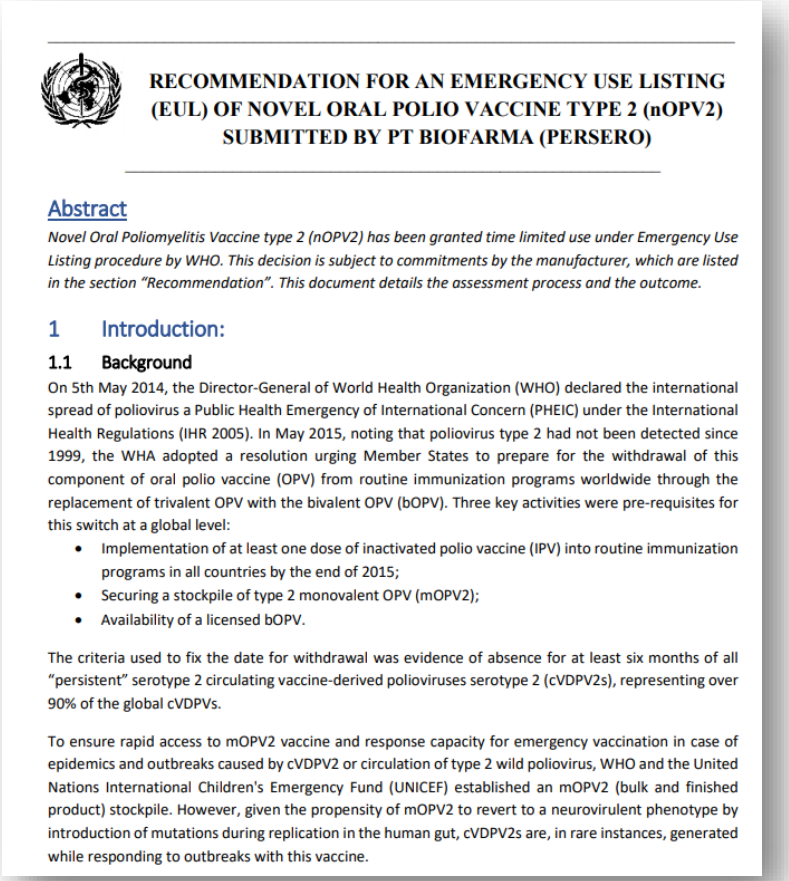
Regulatory Pathway: Emergency Use Listing (EUL)

What is EUL?

The EUL is a **special regulatory pathway that is available for use in Public Health Emergencies of International Concern (PHEIC) such as polio**. It ensures that medical products can be made available as soon as possible in serious public health situations.

The EUL procedure involves months of careful and rigorous analysis by both the WHO Prequalification team and a group of independent experts.

On November 13, 2020, nOPV2 became the first vaccine to be listed under this pathway



RECOMMENDATION FOR AN EMERGENCY USE LISTING (EUL) OF NOVEL ORAL POLIO VACCINE TYPE 2 (nOPV2) SUBMITTED BY PT BIOFARMA (PERSERO)

Abstract

Novel Oral Poliomyelitis Vaccine type 2 (nOPV2) has been granted time limited use under Emergency Use Listing procedure by WHO. This decision is subject to commitments by the manufacturer, which are listed in the section "Recommendation". This document details the assessment process and the outcome.

1 Introduction:

1.1 Background

On 5th May 2014, the Director-General of World Health Organization (WHO) declared the international spread of poliovirus a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (IHR 2005). In May 2015, noting that poliovirus type 2 had not been detected since 1999, the WHA adopted a resolution urging Member States to prepare for the withdrawal of this component of oral polio vaccine (OPV) from routine immunization programs worldwide through the replacement of trivalent OPV with the bivalent OPV (bOPV). Three key activities were pre-requisites for this switch at a global level:

- Implementation of at least one dose of inactivated polio vaccine (IPV) into routine immunization programs in all countries by the end of 2015;
- Securing a stockpile of type 2 monovalent OPV (mOPV2);
- Availability of a licensed bOPV.

The criteria used to fix the date for withdrawal was evidence of absence for at least six months of all "persistent" serotype 2 circulating vaccine-derived polioviruses serotype 2 (cVDPV2s), representing over 90% of the global cVDPVs.

To ensure rapid access to mOPV2 vaccine and response capacity for emergency vaccination in case of epidemics and outbreaks caused by cVDPV2 or circulation of type 2 wild poliovirus, WHO and the United Nations International Children's Emergency Fund (UNICEF) established an mOPV2 (bulk and finished product) stockpile. However, given the propensity of mOPV2 to revert to a neurovirulent phenotype by introduction of mutations during replication in the human gut, cVDPV2s are, in rare instances, generated while responding to outbreaks with this vaccine.

For more on the Emergency Use Listing, please visit the official WHO EUL website: https://extranet.who.int/pqweb/sites/default/files/documents/nOPV2_EUL_recommendation.pdf

Clinical Development: “Container Village”

Pierre Van Damme, Ilse De Coster, Ananda S Bandyopadhyay, Leen Suykens, Patrick Rudelsheim, Pieter Neels, M Steven Oberste, William C Weldon, Ralf Clemens, and Hilde Revets. **Poliopolis**: pushing boundaries of scientific innovations for disease eradication. ***Future Microbiology***. 2019.

CLINICAL ACCELERATION EFFORTS

A global collaboration across multiple agencies supported accelerated generation of clinical data for the EUL submissions by:

- Executing clinical trials in parallel or close succession (adults and children/infants)
- Using satellite sites for rapid, real-time data generation by primary lab to inform trial conduct
- Conducting DSMB data reviews on regular basis to inform age and dose de-escalation while trial/s were on-going
- Generating multiple interim trial reports to enable EUL review
- Implementing five historic control trials in approx. 6 months time ahead of global switch to generate comparator data
- Major scale up and optimization of laboratory capacity with 20,000 stool samples and 5,000 serological samples tested by CDC till date to enable EUL review

CLINICAL DATA FROM KEY TRIALS

THE LANCET

Articles

"M4a"/Phase I study: June 2019

The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study

Pierre Van Damme, Ilse De Coster*, Ananda S Bandyopadhyay, Hilde Revets, Kanchanamala Withanage, Philippe De Smedt, Leen Suykens, M Steven Oberste, William C Weldon, Sue Ann Costa-Clemens, Ralf Clemens, John Modlin, Amy J Weiner, Andrew J Macadam, Raul Andino, Olen M Kew, Jennifer L Konopka-Anstadt, Cara C Burns, John Konz, Rahnuma Wahid, Christopher Gast*

Articles

"M4"/Phase II study: December 2020

Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in healthy adults: two clinical trials

Ilse De Coster, Isabel Leroux-Roels*, Ananda S Bandyopadhyay, Christopher Gast, Kanchanamala Withanage, Katie Steenackers, Philippe De Smedt, Annelies Aerssens, Geert Leroux-Roels, M Steven Oberste, Jennifer L Konopka-Anstadt, William C Weldon, Alan Fix, John Konz, Rahnuma Wahid, John Modlin, Ralf Clemens, Sue Ann Costa Clemens, Novilia S Bachtiar, Pierre Van Damme*

Articles

"M5"/Phase II study: December 2020

Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials

Xavier Sáez-Llorens, Ananda S Bandyopadhyay, Christopher Gast, Tirza De Leon, Rodrigo DeAntonio, Jose Jimeno, Maria Isabel Caballero, Gabriela Aguirre, M Steven Oberste, William C Weldon, Jennifer L Konopka-Anstadt, John Modlin, Novilia S Bachtiar, Alan Fix, John Konz, Ralf Clemens, Sue Ann Costa Clemens, Ricardo Rüttimann

SUMMARY OF nOPV2 CLINICAL TRIAL FINDINGS: DATA SUPPORTING EUL SUBMISSIONS

Favorable general safety / reactogenicity profile of nOPV2

No evidence of any increase in general safety risk compared with mOPV2

nOPV2 appears as immunogenic as mOPV2

nOPV2 demonstrated non-inferior immunogenicity to the historical mOPV2 control groups among infants

nOPV2 appears to induce lower or comparable shedding as mOPV2

Assessment of viral excretion indicates that nOPV2 is unlikely to be shed in a greater rate or quantity as compared to mOPV2, and the cessation of intestinal mucosal viral replication and shedding may be earlier in infants

Data available supports view that nOPV2 is likely to have significantly lower risk of paralysis in humans than mOPV2

No direct way to quantitatively extrapolate to reduced risk of paralysis in humans, the available data support significantly improved genetic and phenotypic stability of shed nOPV2 compared to shed Sabin-2

Bandyopadhyay AS. Clinical data from novel type-2 oral polio vaccine trials and plan for emergency use listing. Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, October 2019 and March – April 2020. https://www.who.int/immunization/sage/meetings/2019/october/Bandyopadhyay_polio_sage_october_2019.pdf?ua=1. Summary: http://polioeradication.org/wp-content/uploads/2020/05/Clinical-development-summary-nOPV2-20200521.pdf

MANUFACTURING ACCELERATION EFFORTS

Bio Farma has achieved several key milestones for accelerated stockpile build-up for the global program:

Completed scale-up from Pilot Scale to Commercial Scale Manufacturing in < 10 months and implemented change from 20- to 50-dose vial to amplify acceleration efforts

Quickly pivoted to address WHO PQ questions about variants by increasing fill target to 5.4 in order to:

1. Compensate for genetic variants
2. Ensure sufficient antigen to meet target dose
3. Meet VVM2 requirement

Completed production of drug substance (DS) corresponding to 200 M doses in September 2020

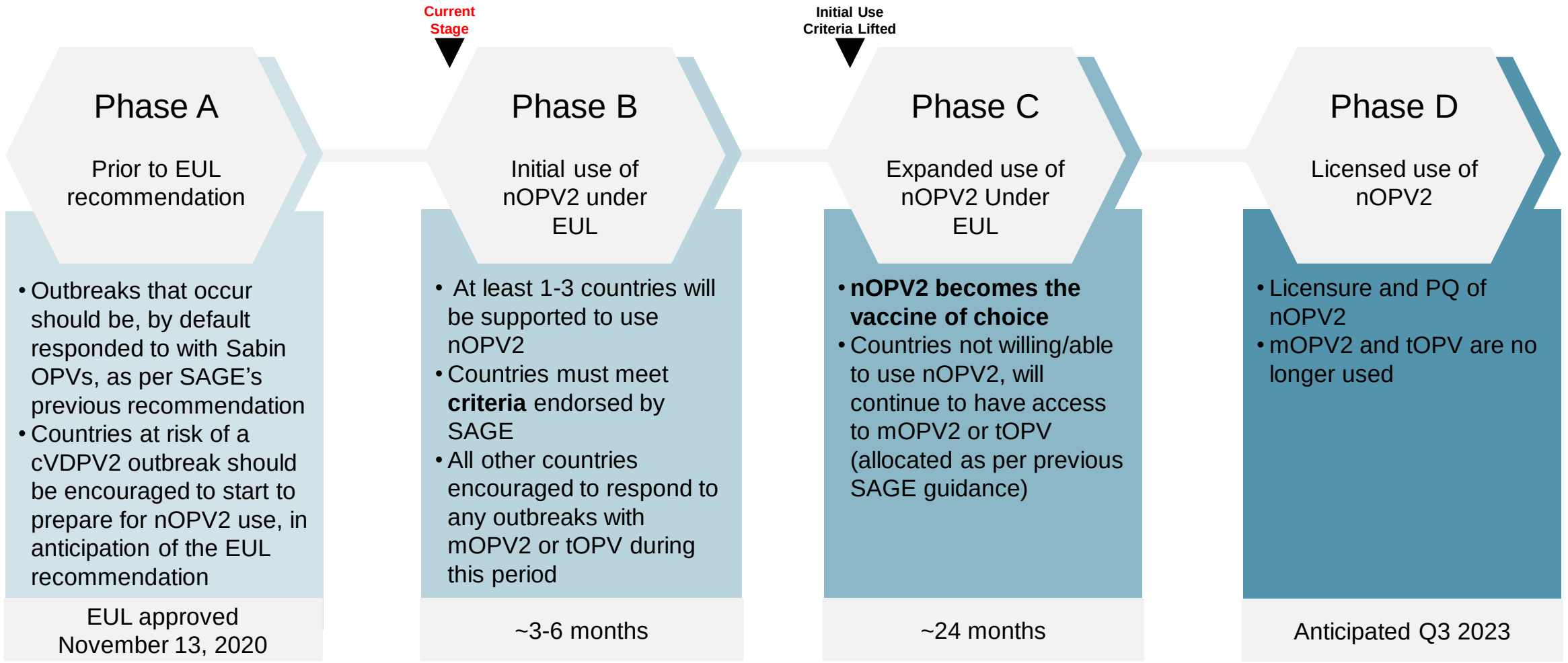
Commercial drug product (DP) production, packaging, and labeling of 200 M doses well underway and will continue through early 2021

- Meeting UNICEF demand for 40 mds total during the initial use phase
  - 28 mds released in December
  - 12 mds released in January
- Regular releases starting after the initial use phase to continue to meet outbreak response (GPEI) demand

Slide/information courtesy: Rachel Lee/Rayasam Prasad; BMGF

PLAN FOR USE OF nOPV2 FOR OUTBREAK RESPONSE

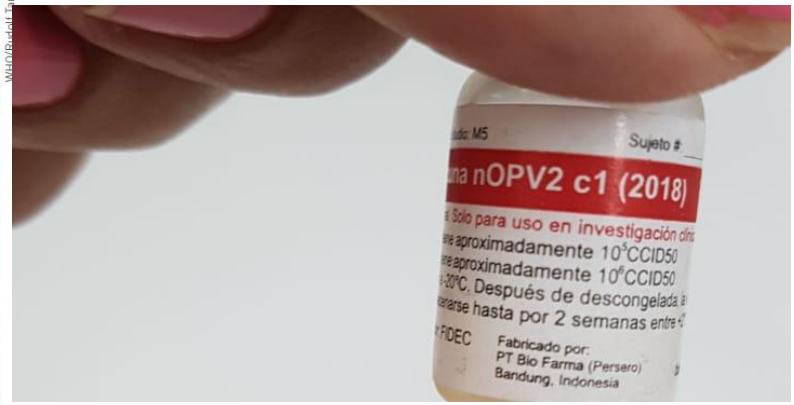
SAGE endorsed framework for the use of nOPV2



“Vaccination”

Inactivated poliovirus vaccine (IPV)

Sabin Oral polio vaccine (OPV)



Novel oral polio vaccine (nOPV)

Vaccination: Adventure Sport ?

Photo: Ananda Bandyopadhyay, Bill & Melinda Gates Foundation

SUMMARY

- *Expanding spread of circulating VDPVs pose a major threat to the completeness of polio eradication and necessitates urgent public health action.*
- *Novel OPVs with enhanced genetic stability linked with specific attenuations hold the promise of interrupting these outbreaks without the same risk of seeding new outbreaks compared to Sabin OPV2.*
- *A concerted development effort with multiple global agencies enabled rapid completion of uniquely designed phase I / II studies and at-scale at-risk manufacturing of the vaccine.*
- *EUL approval paves the way for early use of the vaccine in key areas as early as Q1 2021.*
- *Streamlining of regulatory and manufacturing processes will be key to inform timely development and roll-out process of future tools for Public Health Emergencies of International Concern.*

ACKNOWLEDGMENT

- Polio and Vaccine Development/Surveillance teams at the Gates Foundation
- GPEI and its nOPV2 Working Group
- Clinical development and manufacturing partners, including FIDEC, University of Antwerp, Bio Farma, US CDC, PATH and others.

Many others..