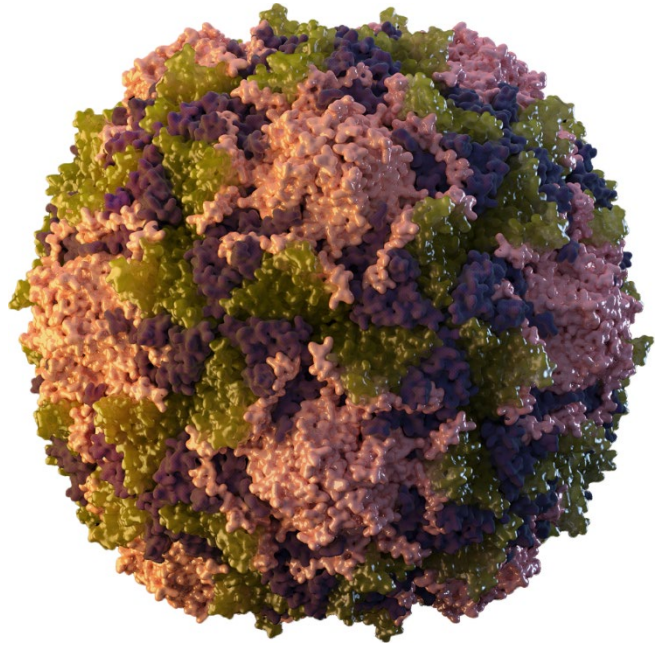
Considerations for the Potential Use of Novel Type 2 Oral Poliovirus Vaccine (nOPV2) as an Outbreak Control Measure in the United States



Sarah Kidd, MD, MPH

ACIP Meeting

February 28, 2024

Polio Work Group Members

- ACIP voting members
  - Oliver Brooks (Chair)
  - Lynn Bahta
  - Sybil Cineas

- Liaisons
  - Lynn Fisher, American Academy of Family Physicians
  - Chandy C. John, American Academy of Pediatrics
  - Sandra Fryhofer, American Medical Association
  - Kathy Kudish, Association of Immunization Managers
  - Marcus Plescia, Association of State and Territorial Health Officials
  - Paul R. Cieslak, Council of State and Territorial Epidemiologists
  - Christine Hahn, Council of State and Territorial Epidemiologists
  - Tina Q. Tan, Infectious Diseases Society of America
  - Adenike Shoyinka, Infectious Diseases Society of America
  - Mary Wilson, International Society of Travel Medicine
  - Jaqueline Lawler, National Association of County and City Health Officials
  - Kathy Edwards, Pediatric Infectious Diseases Society
  - Joseline Zafack, Public Health Agency of Canada*

- Consultants
  - Edwin Asturias
  - Doug E Campos-Outcalt*
  - Emily Lutterloh
  - Jennifer Rosen
  - Eli Rosenberg

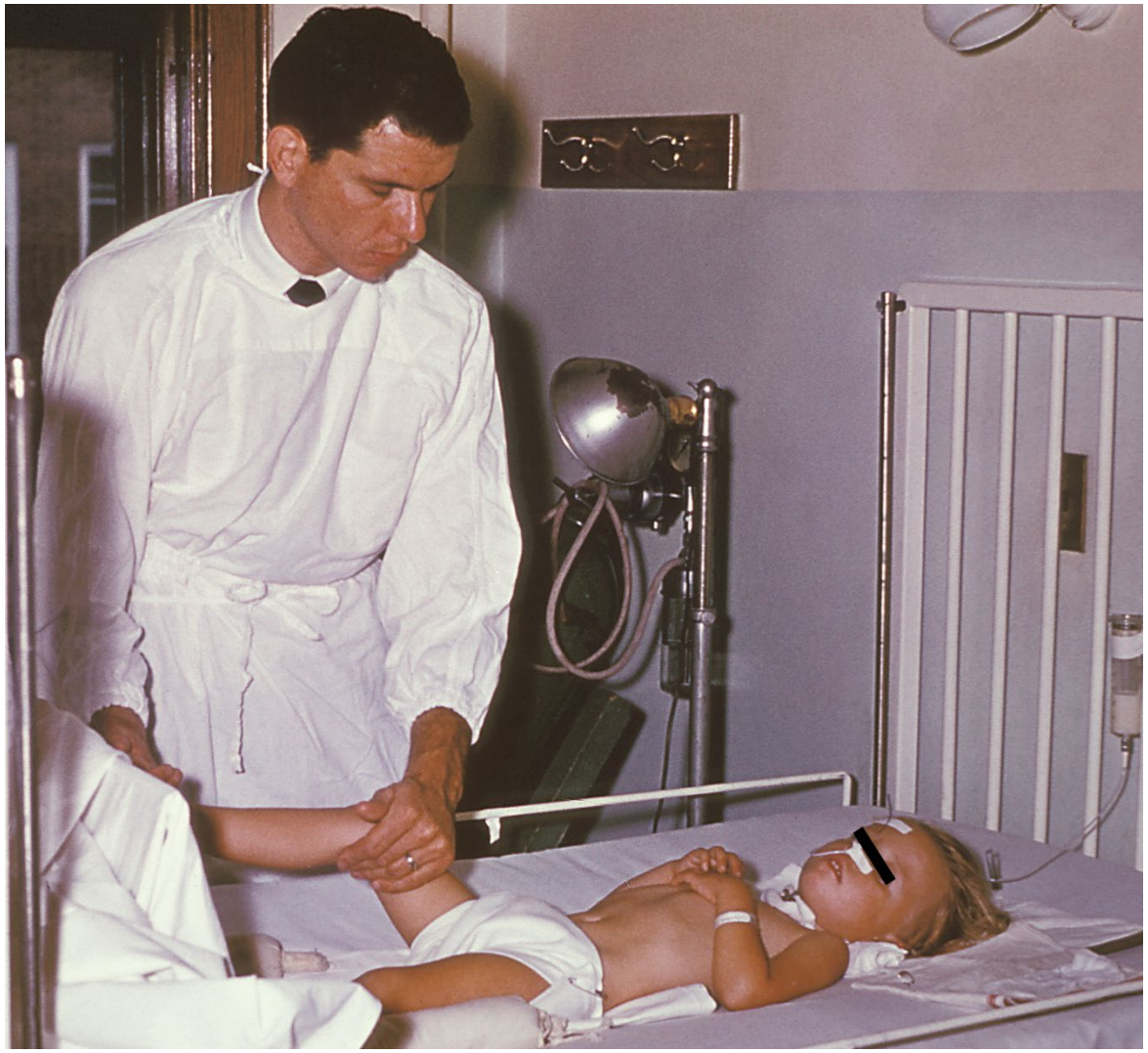
- FDA*
  - Robin Levis

- CDC*
  - Cara Burns
  - Thomas Clark
  - Miranda Delahoy
  - Brian Edlin
  - Concepcion Estivariz
  - Halle Getachew
  - Sarah Kidd
  - Janelle King
  - Adriana Lopez
  - M. Steve Oberste

*In the event of a Work Group poll, CDC, FDA, and Public Health Agency of Canada members are not included.

Public Health Problem

- Poliovirus infection can cause poliomyelitis and lifelong paralysis
  - Paralytic disease occurs in <1% of infections (varies by serotype)
  - Non-paralytic clinical illness occurs in ~25%, including 1%–5% with aseptic meningitis
  - Approximately 75% of infections are asymptomatic



Poliovirus Serotypes

- Three poliovirus serotypes: type 1, type 2, and type 3
- Immunity to one serotype does not result in significant immunity to other serotypes
- Ratio of paralytic cases to infections varies by serotype
  - Type 1: approximately 1/190
  - Type 2: approximately 1/1900
  - Type 3: approximately 1/1100

Nathanson N, Kew OM. Am J Epidemiol 2010;172:1213–29.

Poliovirus is highly infectious

- Person-to-person spread of poliovirus occurs via the **fecal-oral** or **oral-oral** routes
  - Fecal-oral is the most important transmission pathway in settings with suboptimal hygiene and sanitation

- Patients are most infectious during days immediately before and after onset of symptoms, but virus **may remain present in stool for up to 6 weeks**, sometimes longer
  - **Individuals with minor symptoms or no illness can shed virus**

Inactivated Polio Vaccine (IPV)

- Only polio vaccine used in the US
- Contains inactivated polioviruses types 1, 2, and 3 polioviruses
- Induces effective humoral immunity → prevents paralysis
- Induces some **nasopharyngeal mucosal immunity,** but **limited intestinal immunity**

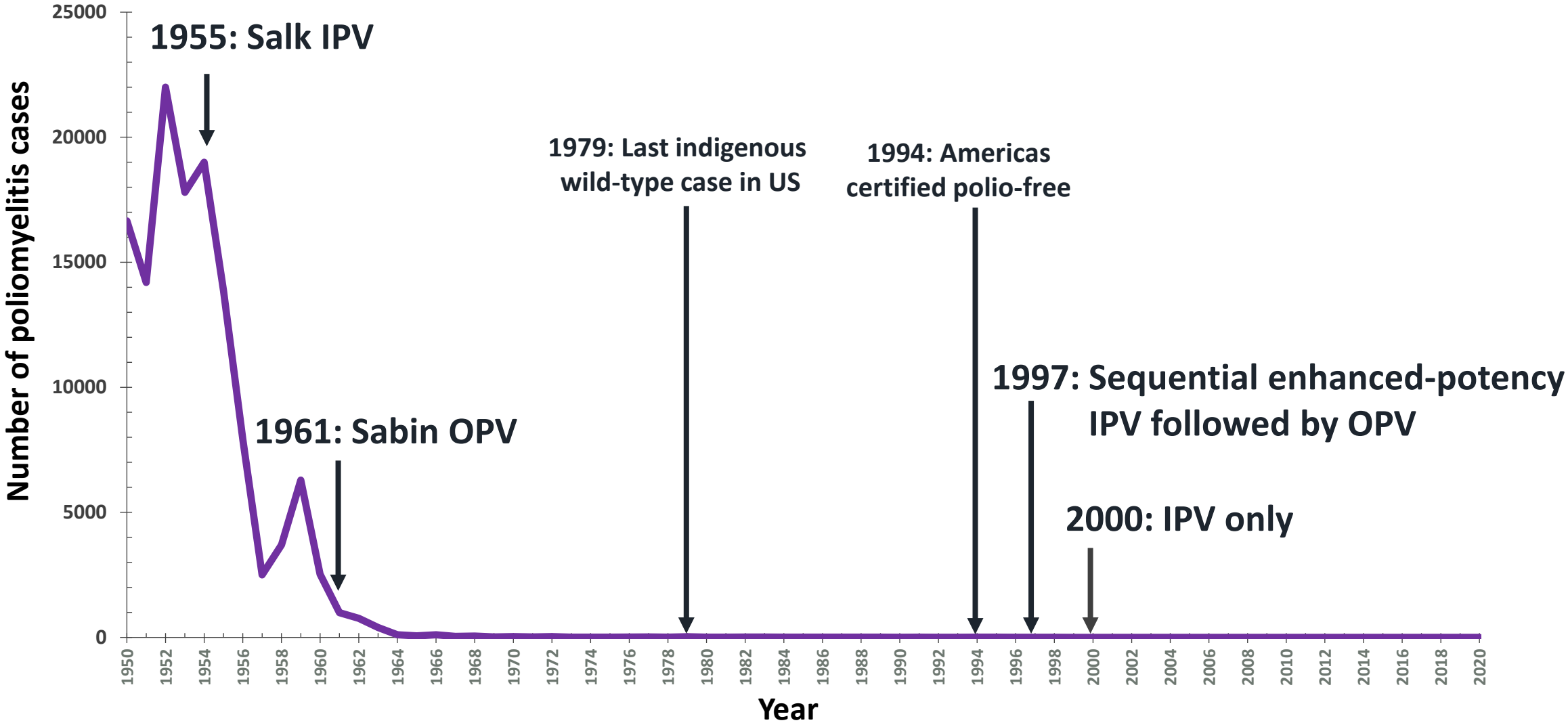
Oral Polio Vaccine (OPV)

- Live attenuated vaccine (Sabin)
  - Trivalent OPV (tOPV): contains types 1, 2, and 3
  - Bivalent OPV (bOPV): contains types 1 and 3
  - Monovalent OPV (mOPV#): contains single type (#=1, 2, or 3)
- Replicates in gut, is shed in stool
- Induces humoral and mucosal immunity
  - **Prevents paralysis and transmission** of poliovirus
- Historical vaccine of choice for countries with outbreaks
- **Attenuated virus can revert to a neurovirulent form that causes paralysis**

Novel Type 2 Oral Polio Vaccine (nOPV2)

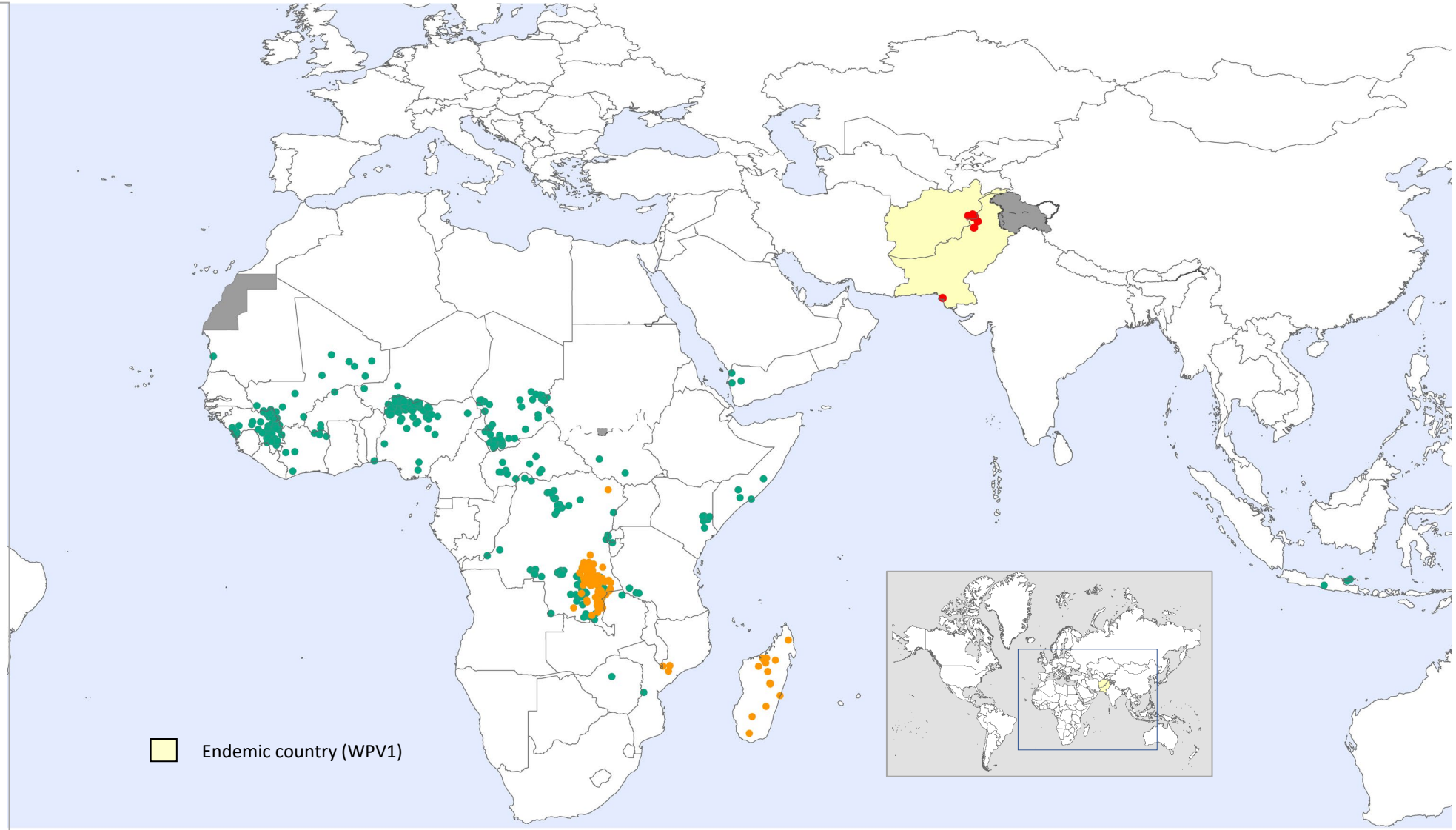
- Novel, next-generation version of monovalent type 2 oral polio vaccine (nOPV2)
- **Designed to be more genetically stable, less likely to revert to neurovirulent form**
- March 2021–December 2023:
  - Almost 1 billion doses administered in 35 countries under WHO Emergency Use Listing (EUL) approval
- December 2023: Earned WHO prequalification

Paralytic polio decreased rapidly in the US after introduction of polio vaccine



Global Paralytic WPV1 and cVDPV Cases[1], Previous 12 Months[2]

WPV1 cases (latest onset)		
Pakistan	5	24-Oct-23
Afghanistan	6	04-Sep-23
cVDPV1 cases (latest onset)		
DR Congo	90	24-Nov-23
Mozambique	3	06-Nov-23
Madagascar	17	16-Sep-23
cVDPV2 cases (latest onset)		
Niger	2	11-Dec-23
Indonesia	3	06-Dec-23
Nigeria	80	03-Dec-23
Zimbabwe	1	02-Dec-23
Guinea	46	28-Nov-23
Chad	49	26-Nov-23
Côte d'Ivoire	6	22-Nov-23
DR Congo	87	19-Nov-23
Yemen	4	17-Nov-23
Tanzania	3	16-Nov-23
Mali	12	06-Nov-23
South Sudan	2	04-Nov-23
Mauritania	1	17-Oct-23
CAR	10	07-Oct-23
Mozambique	1	28-Sep-23
Somalia	4	16-Sep-23
Kenya	8	21-Aug-23
Burundi	1	15-Jun-23
Burkina Faso	2	04-Jun-23
Zambia	1	03-Apr-23
Benin	2	15-Mar-23



[1]Excludes viruses detected from environmental surveillance; [2]Onset of paralysis: 21 Feb. 2023 to 20 Feb. 2024

Data in WHO HQ as of 20 Feb. 2024

https://polioeradication.org/polio-today/polio-now/

Paralytic Polio Case in New York State, July 2022

- A case of paralytic polio caused by vaccine-derived poliovirus type 2 (VDPV2) was confirmed in an unvaccinated young adult from Rockland County, New York, on July 21, 2022
- Genetic sequencing has indicated a linkage to polioviruses collected in wastewater in Israel, United Kingdom, and Canada
- Rockland County has reported overall low vaccine coverage for over 20 years
  - In summer 2022, 60% of children under 2 years of age had received 3 doses of IPV (zip code level as low as 37%)

- No additional paralytic cases were identified

Wastewater Testing for Poliovirus in New York

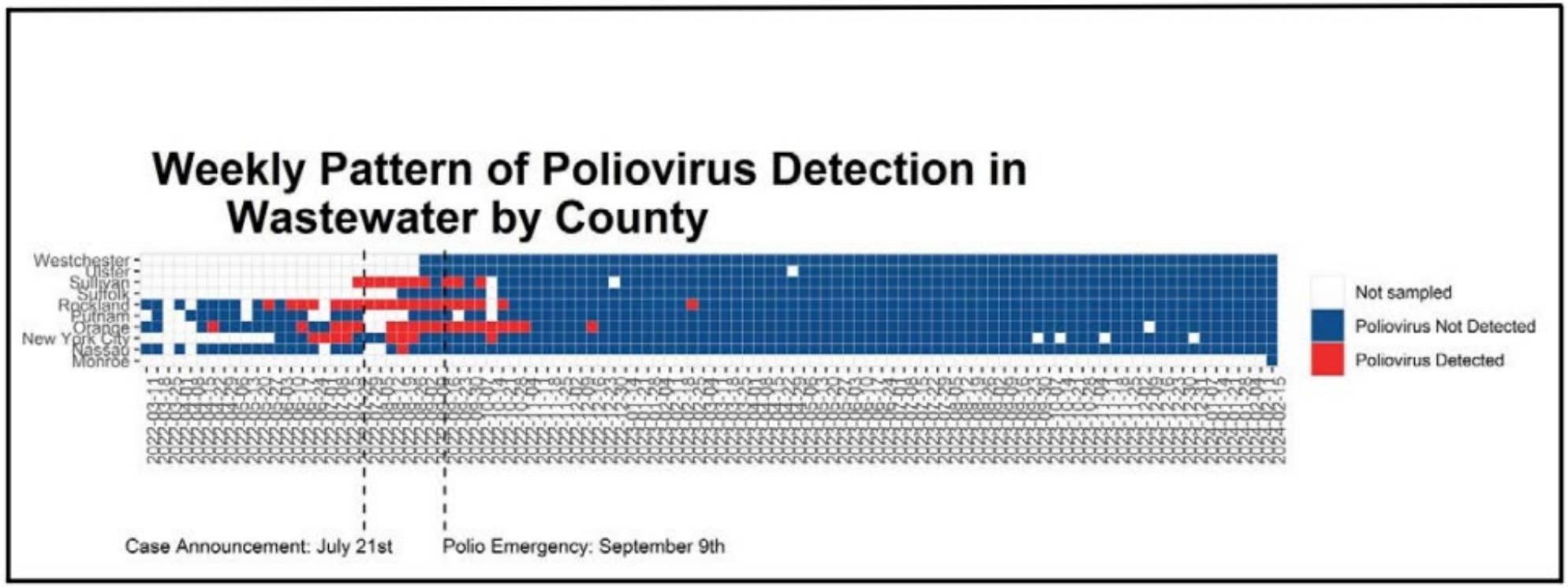
- Poliovirus type 2 genetically linked to the case detected in wastewater samples in New York (Rockland, Orange, Sullivan, and Nassau counties and New York City)
- Retrospective testing detected poliovirus as early as April 2022
- Only 2 positive samples since November 1, 2022 (most recent February 22, 2023)
- No detections in samples collected in last 11+ months (since February 2023)

https://www.health.ny.gov/diseases/communicable/polio/docs/waste_water_surveillance_report.pdf

NEW YORK STATE | Department of Health

FEBRUARY 26, 2024

Weekly Poliovirus Detection in Wastewater By County



Poliovirus detected indicates samples with any detection of a poliovirus Type 2, including samples that have not been definitively genetically linked to the individual case in Rockland County.

https://www.health.ny.gov/diseases/communicable/polio/docs/waste_water_surveillance_report.pdf

Outbreak Response Vaccination

- 2022 New York Strategy: Identify unvaccinated and undervaccinated persons, provide catch-up vaccination with IPV

- WHO recommendations for poliovirus outbreaks in countries with exclusive IPV vaccination and high sanitation and hygiene:
  - Conduct a timely outbreak response with IPV only if poliovirus transmission is confined in a well-defined population group or geographic area.
  - If transmission persists, consider an OPV response.

- Work Group asked to discuss considerations for potential use of nOPV2 as an outbreak response measure in the US

Theoretical Policy Question for Work Group

- **Should nOPV2 be used in combination with a catch-up IPV campaign during a future type 2 poliovirus outbreak in the US?**
  - **Population:** Persons living in area with circulating poliovirus
  - **Intervention:** nOPV2 vaccination for all + catch-up IPV vaccination for un- or under-vaccinated
  - **Comparison:** Catch-up IPV vaccination only
  - **Outcomes:**
    - Prevention of paralytic poliomyelitis
    - Extent and duration of poliovirus circulation in the community
    - Serious adverse effects, including vaccine-associated paralytic polio
    - Possible introduction of new vaccine-derived poliovirus type 2

ACIP Evidence to Recommendations (EtR) Framework

- Problem
  - Is the problem of public health importance?
- Benefits & Harms
  - How substantial are the desirable anticipated effects?
  - How substantial are the undesirable anticipated effects?
  - Do the desirable effects outweigh the undesirable effects?
  - What is the overall certainty of this evidence for the critical outcomes?
- Values
  - Does the target population feel that the desirable effects are large relative to the undesirable effects?
  - Is there important uncertainty about or variability in how much people value the main outcome?
- Acceptability
  - Is the intervention acceptable to key stakeholders?
- Resource Use
  - Is the intervention a reasonable and efficient allocation of resources?
- Equity
  - What would be the impact on health equity?
- Feasibility
  - Is the intervention feasible to implement?

EtR Domain: Public Health Problem

Work group interpretation

Is paralytic poliomyelitis a problem of public health importance?

No	Probably no	Probably yes	**Yes**		Varies	Don't know

Effectiveness:
High Rates of Seroconversion Following nOPV2

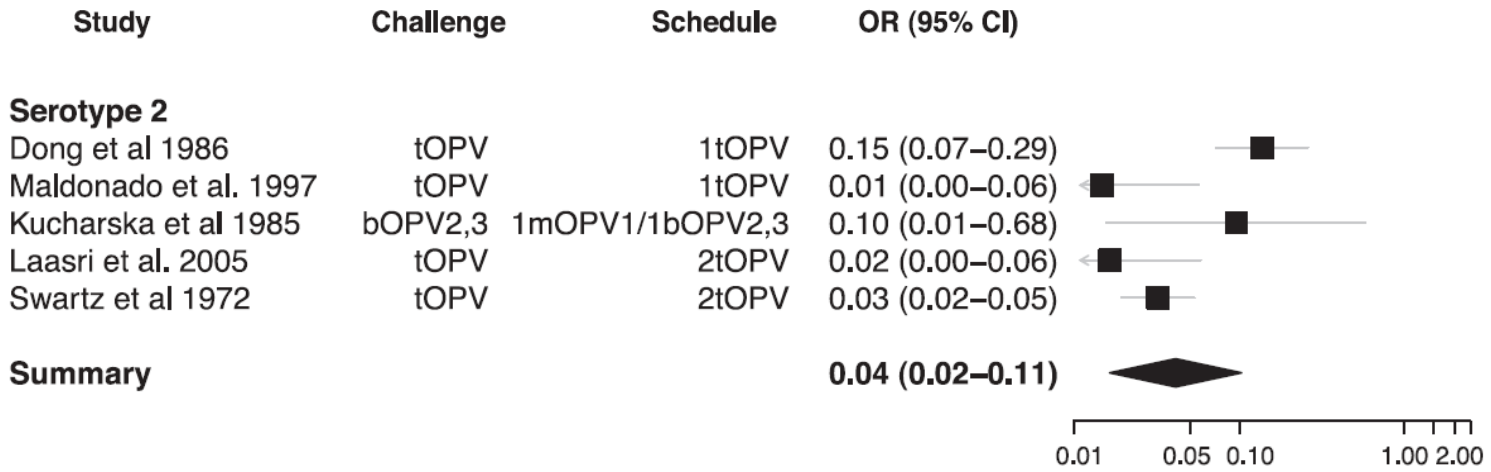
- Seroconversion among infants who had received 1 dose of IPV (Sáez-Llorens et al)
  - 86% 28 days after 1 dose
  - 98% 28 days after 2 doses

- Seroconversion among vaccine-naïve infants (Zaman et al; Wilkinson et al)
  - 46%–64% 28 days after 1 dose
  - 86%–90% 28 days after 2 doses

Sáez-Llorens et al. Lancet 2021;397:27–38.
Zaman et al. Lancet 2023;401:131–39.
Wilkinson et al. Lancet Infect Dis 2023;23:1062–71.

Effectiveness: Mucosal Immunity

- Sabin OPV2 reduces odds of fecal shedding of type 2 virus after a challenge (Hird and Grassly)



- In small Phase 1 study among adults previously vaccinated with IPV (Brickley et al)
  - 33% had detectable stool neutralization titer against PV2 at 28 days after 1 dose of nOPV2
  - 15% had detectable PV2-specific IgA in stool at 28 days after 1 dose of nOPV2

Hird and Grassly. PLoS Pathogens 2012;8(4):e1002599.

Brickley et al. J Infect Dis 2022;26:287–91.

Fecal Shedding of nOPV2 Virus After 1st Dose of nOPV2

Days after 1st dose of nOPV2	% of Infants* with Detectable nOPV2 Virus in Stool	
	Measured by PCR	Measured by Culture
7 days	85%	40%
14 days	52%	17%
28 days	40% - 57%	1% - 14%

*Includes newborn vaccine-naïve infants and infants who had previously received 3 bOPV doses and 1 IPV dose

Zaman et al. Lancet 2023;401:131–39.
Gast et al. J Infect Dis 2022;226:852–61.

Risk of Vaccine-Associated Paralytic Polio (VAPP) Following nOPV2

- nOPV2 more genetically stable than Sabin OPV2, less likely to regain neurovirulence

- Risk of VAPP in recipients
  - nOPV2: estimated 0.07 cases per million recipients (1 per 14.3M recipients)
  - Sabin OPV: 0.25–4 cases per million recipients (1 per 0.25M–4M recipients)
  - Risk highest in unimmunized children receiving 1st dose of OPV or in immunocompromised persons
  - Could be mitigated by limiting nOPV2 administration to persons who had previously received ≥1 IPV dose

Bandyopadhyay and Zipursky. Lancet ID 2023;23:e67–71.

Risk of Introducing a New Circulating Vaccine-Derived Poliovirus (cVDPV) Following nOPV2

- >700 million nOPV2 doses administered worldwide in 32 countries since March 2021
  - At least **7** separate emergences of new cVDPV2 linked to nOPV2 (cVPDV2-n)
  - At least **61** detected paralytic cases associated with cVDPV2-n

- Estimates: nOPV2 is 80% less likely than mOPV2 to seed new cVDPV2

- Risk of new cVDPV is highest when campaign coverage is low in a population with low immunity against polioviruses

Davlantes et al. MMWR 2023;72(38):1041–1042.
https://polioeradication.org/wp-content/uploads/2024/01/GPEI-nOPV2-Factsheet-20240105.pdf

For Individual nOPV2 Recipients

Potential effects of adding nOPV2 to the IPV outbreak response

- Most recipients will already be fully vaccinated with 3–4 doses of IPV, already protected against paralytic disease

- Anticipated benefits of nOPV2 to recipient
  - Higher anti-poliovirus type 2 antibody titer
  - Increased odds of mucosal immunity to poliovirus type 2
  - For undervaccinated persons: additional protection against paralytic disease
  - For previously vaccinated persons: unlikely clinical benefit

- Potential harms of nOPV2 to recipient
  - Extremely low, but non-zero risk of VAPP (<1 case per 14.3 million doses administered)
  - Risk of chronic infection if given to child with unrecognized immunocompromise

At the Population Level

Potential effects of adding nOPV2 to the IPV outbreak response

- Potential benefits to population
  - Decreased transmission among nOPV2 recipients → outbreak ends earlier → fewer paralytic cases
  - Passive vaccination of unvaccinated → decreased transmission and fewer paralytic cases
- Potential harms to population
  - Passive vaccination of unvaccinated → risk of VAPP among unvaccinated
  - Possible ongoing transmission of nOPV2 virus → new cVDPV2-n
  - Possible chronic infection in immunocompromised
- Magnitude of benefits and harms depends on nOPV2 coverage, extent of mixing between nOPV2 recipients and unvaccinated (and immunocompromised)

Modeling:
Expected Paralytic Cases Under Different Mixing Scenarios for a cVDPV2 Outbreak Similar to 2022 New York Outbreak

	Modeled cVDPV2 cases				
Vaccine used for outbreak response	IPV	None	mOPV2	nOPV2 best	nOPV2 worst
Subpopulation isolation	0.88	1.89	0.64	0.55	0.67
No isolation	0.64	0.86	0.51	0.44	0.53
Partial isolation	0.35	0.39	0.30	0.27	0.31

Note: Model assumed the number of vaccine doses administered was same as number of IPV doses administered during 2022 New York outbreak.

Abbreviations: *IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; mOPV, monovalent OPV (specific for each type), nOPV, novel OPV (specific for each type, see text for characteristics of nOPV best and nOPV worst).*

Thompson et al. Vaccine 2024;42:819–27.

Modeling:
Expected Paralytic Cases Under Different Mixing Scenarios for cVDPV1 Outbreak and Hypothetical Novel Type 1 OPV

	Modeled cVDPV1 cases				
Vaccine used for outbreak response	IPV	None	mOPV1	nOPV1 best	nOPV1 worst
Subpopulation isolation	56	65	45	22	47
No isolation	130	179	91	26	97
Partial isolation	36	163	23	11	25

Note: Model assumed the number of vaccine doses administered was same as number of IPV doses administered during 2022 New York outbreak.

Abbreviations: *IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; mOPV, monovalent OPV (specific for each type), nOPV, novel OPV (specific for each type, see text for characteristics of nOPV best and nOPV worst).*

Thompson et al. Vaccine 2024;42:819–27.

EtR Domain: Benefits & Harms

Work group interpretation

How substantial are the desirable anticipated effects of nOPV2* on the individual and population levels?

Minimal	**Small**	Moderate	Large		Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

EtR Domain: Benefits & Harms

Work group interpretation

How substantial are the undesirable anticipated effects of nOPV2* on the individual and population levels?

Minimal	**Small**	**Moderate**	Large		Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

EtR Domain: Benefits & Harms

Work group interpretation

Do the desirable effects of nOPV2* outweigh the undesirable effects on the individual and population levels?

Yes, favors nOPV2	**No, favors IPV only**	Favors either option equally	Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

Implementing an nOPV2 Program in the US

- Expanded access investigational new drug application (EA-IND)

- Requires application to FDA and FDA authorization

- If implemented, nOPV2 EA-IND program must include
  - Signed informed consent by vaccinees and/or guardians
  - System for monitoring vaccine safety
  - Enhanced surveillance for possible VAPP cases
  - Environmental surveillance for new cVDPV2s
  - System for tracking and accounting for every dose for containment purposes

EtR Domain: Resource Use

Work group interpretation

Is an nOPV2 campaign* a reasonable and efficient allocation of resources?

No	**Probably no**	Probably yes	Yes		Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

EtR Domain: Feasibility

Work group interpretation

Is a nOPV2 campaign* feasible to implement?

No	Probably no	**Probably yes**	Yes		Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

Values and Acceptability Considerations

- Trivalent OPV (tOPV) was removed from vaccination schedule in 2000 and replaced with IPV because any risk of VAPP was deemed unacceptable; this might be barrier to acceptance of a new OPV vaccine
- The need for signed informed consent will likely be a deterrent
- Unclear whether general public will accept an OPV if they are already protected from paralytic infection by IPV
- Unclear whether population most at risk (those with low childhood vaccination coverage and high rates of vaccine skepticism) will accept an OPV vaccine
- Perceptions of risk and vaccine acceptance might shift in outbreak setting, if there is >1 paralytic case in a community

EtR Domain: Values of Target Population

Work group interpretation

Does the target population feel that the desirable effects of nOPV2* are large relative to undesirable effects?

No	**Probably no**	Probably yes	Yes		Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

EtR Domain: Values of Target Population

Work group interpretation

Is there important uncertainty or variability in how much people value the main outcomes?

Important uncertainty or variability	**Probably important uncertainty or variability**	**Probably not important uncertainty or variability**	No important uncertainty or variability		No known undesirable outcomes

EtR Domain: Acceptability to Key Stakeholders

Work group interpretation

Is nOPV2* acceptable to key stakeholders?

No	**Probably no**	**Probably yes**	Yes		**Varies**	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

Equity Considerations

Globally

- Single manufacturer (BioFarma, Indonesia)
- Managed via a global stockpile
- Supply shortages have occurred in the past
- In US, IPV is readily available, provides protection against paralysis from cVDPV2
- In many countries with cVDPV2 outbreaks, limited protection against cVDPV2 unless there are nOPV2 or mOPV2 campaigns

In US

- Preventing transmission protects unvaccinated/undervaccinated and immunocompromised

EtR Domain: Equity

Work group interpretation

What would be the impact of an nOPV2 campaign* in the US on health equity?

Reduced equity	Probably reduced equity	**Probably no impact**	Probably increased equity	Increased equity	Varies	Don't know

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

Work Group Judgement: Balance of Consequences

Using nOPV2 as an outbreak control measure in the US*

Undesirable consequences **clearly** outweigh desirable consequences in most settings	**Undesirable consequences probably outweigh desirable consequences in most settings**	**The balance between desirable and undesirable consequences is closely balanced or uncertain**	**Desirable** consequences **probably** outweigh undesirable consequences in most settings	**Desirable** consequences **clearly** outweigh undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

*during a VDPV2 outbreak, when nOPV2 given in addition to any IPV doses received as part of routine immunization

Summary
Use of nOPV2 During a cVDPV2 Outbreak in the US

- At this time, the work group believes the **undesirable consequences probably outweigh OR are closely balanced** with the desirable consequences.
- Main considerations included
  - IPV is readily available in the US and protects against paralytic disease
  - Primary benefit of adding nOPV2 to an outbreak response would be to reduce transmission of outbreak virus, reduce risk of paralytic disease in undervaccinated or immunocompromised persons
  - Differences of opinion regarding the value of reducing asymptomatic transmission or ending asymptomatic transmission earlier during outbreak
  - Extremely low, but non-zero risk of VAPP (est. 1 per 14.3 million recipients) or new cVDPV2
  - Uncertainty about public and stakeholder acceptance of nOPV2
- Balance of undesirable consequences vs. desirable consequences might shift in the future depending on size and scope of outbreak

Questions and Discussion