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

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ACIP Meeting
February 28, 2024
Polio Work Group Members

- **ACIP voting members**
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  - Chandy C. John, American Academy of Pediatrics
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*In the event of a Work Group poll, CDC, FDA, and Public Health Agency of Canada members are not included.*
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
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

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

- 1955: Salk IPV
- 1961: Sabin OPV
- 1979: Last indigenous wild-type case in US
- 1994: Americas certified polio-free
- 1997: Sequential enhanced-potency IPV followed by OPV
- 2000: IPV only
Global Paralytic WPV1 and cVDPV Cases¹, Previous 12 Months²

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)

Data in WHO HQ as of 20 Feb. 2024

¹Excludes viruses detected from environmental surveillance; ²Onset of paralysis: 21 Feb. 2023 to 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)

Weekly Poliovirus Detection in Wastewater By County

Weekly Pattern of 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.

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
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?
Work group interpretation

Is paralytic poliomyelitis a problem of public health importance?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>
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

Effectiveness: Mucosal Immunity

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Challenge</th>
<th>Schedule</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dong et al 1986</td>
<td>1OPV</td>
<td>1OPV</td>
<td>0.15 (0.07–0.29)</td>
</tr>
<tr>
<td>Maldonado et al. 1997</td>
<td>1OPV</td>
<td>1OPV</td>
<td>0.01 (0.00–0.06)</td>
</tr>
<tr>
<td>Kucharska et al 1985</td>
<td>bOPV2,3</td>
<td>1mOPV1/1bOPV2,3</td>
<td>0.10 (0.01–0.68)</td>
</tr>
<tr>
<td>Laasri et al. 2005</td>
<td>tOPV</td>
<td>2tOPV</td>
<td>0.02 (0.00–0.06)</td>
</tr>
<tr>
<td>Swartz et al 1972</td>
<td>tOPV</td>
<td>2tOPV</td>
<td>0.03 (0.02–0.05)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td><strong>0.04 (0.02–0.11)</strong></td>
</tr>
</tbody>
</table>

- 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

## Fecal Shedding of nOPV2 Virus After 1\textsuperscript{st} Dose of nOPV2

<table>
<thead>
<tr>
<th>Days after 1\textsuperscript{st} dose of nOPV2</th>
<th>% of Infants* with Detectable nOPV2 Virus in Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Measured by PCR</td>
</tr>
<tr>
<td>7 days</td>
<td>85%</td>
</tr>
<tr>
<td>14 days</td>
<td>52%</td>
</tr>
<tr>
<td>28 days</td>
<td>40% - 57%</td>
</tr>
</tbody>
</table>

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

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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

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.
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 $\rightarrow$ outbreak ends earlier $\rightarrow$ fewer paralytic cases
- Passive vaccination of unvaccinated $\rightarrow$ decreased transmission and fewer paralytic cases

▲ Potential harms to population
- Passive vaccination of unvaccinated $\rightarrow$ risk of VAPP among unvaccinated
- Possible ongoing transmission of nOPV2 virus $\rightarrow$ 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

<table>
<thead>
<tr>
<th>Vaccine used for outbreak response</th>
<th>Modeled cVDPV2 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPV</td>
<td>None</td>
</tr>
<tr>
<td>Subpopulation isolation</td>
<td>0.88</td>
</tr>
<tr>
<td>No isolation</td>
<td>0.64</td>
</tr>
<tr>
<td>Partial isolation</td>
<td>0.35</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Subpopulation isolation</th>
<th>Modeled cVDPV1 cases</th>
<th>Vaccine used for outbreak response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPV</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>mOPV1</td>
<td>nOPV1 best</td>
</tr>
<tr>
<td></td>
<td>nOPV1 worst</td>
<td></td>
</tr>
<tr>
<td>No isolation</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>179</td>
</tr>
<tr>
<td>Partial isolation</td>
<td>36</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

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).
**EtR Domain: Benefits & Harms**

Work group interpretation

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

<table>
<thead>
<tr>
<th>Minimal</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

* 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?

<table>
<thead>
<tr>
<th>Minimal</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

*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?

<table>
<thead>
<tr>
<th>Yes, favors nOPV2</th>
<th><strong>No, favors IPV only</strong></th>
<th>Favors either option equally</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

*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?**

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

*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?

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

*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?**

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

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* 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?

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

*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
Work group interpretation

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

<table>
<thead>
<tr>
<th>Reduced equity</th>
<th>Probably reduced equity</th>
<th><strong>Probably no impact</strong></th>
<th>Probably increased equity</th>
<th>Increased equity</th>
<th>Varies</th>
<th>Don’t know</th>
</tr>
</thead>
</table>

* 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 | 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 |

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*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