Screening for Long-term Poliovirus Excretion Among Children With Primary Immunodeficiency Disorders: Preparation for the Polio Posteradication Era in Bangladesh

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Background. Persons with primary immune deficiency disorders (PIDD) who receive oral poliovirus vaccine (OPV) may transmit immunodeficiency-associated vaccine-derived polioviruses (iVDPVs) and cause paralytic polio. The objective of this study was to identify children with PIDD in Bangladesh, and estimate the proportion with chronic poliovirus excretion.

Methods. Patients admitted at 5 teaching hospitals were screened for PIDD according to standardized clinical case definitions. PIDD was confirmed by age-specific quantitative immunoglobulin levels. Stool specimens were collected from patients with confirmed PIDD.

Results. From February 2011 through January 2013, approximately 96,000 children were screened, and 53 patients were identified who met the clinical case definition for PIDD. Thirteen patients (24%) had age-specific quantitative immunoglobulins results that confirmed PIDD. Of these, 9 (69%) received OPV 3–106 months before stool specimen collection. Among 11 patients, stool specimens from 1 patient tested positive for polioviruses 34 months after OPV ingestion. However, the poliovirus isolate was not available for genetic sequencing, and a subsequent stool specimen 45 days later was negative.

Conclusions. The risk of chronic poliovirus excretion among children with PIDD in Bangladesh seems to be low. The national polio eradication program should incorporate strategies for screening for poliovirus excretion among patients with PIDD.

Keywords. polio; primary immunodeficiency disorders; oral poliovirus vaccine; vaccine associated paralytic polio; immunodeficiency-associated vaccine-derived poliovirus (iVDPV); screening.

Polio can cause potentially fatal poliomyelitis that historically has been a major cause of permanent disability. The number of new paralytic poliomyelitis cases has decreased from 350,000 in 1988, at the beginning of the Global Polio Eradication Initiative, to 406 reported cases in 2013 [1]. Because it is inexpensive and easily administered, the live attenuated oral poliovirus vaccine (OPV) has been the vaccine of choice for polio eradication in most parts of the world. The vaccine virus spreads from vaccine recipients to others, resulting in community protection in contacts not directly vaccinated.

Parallel to the benefits, OPV ingestion poses a rare risk of developing vaccine-associated paralytic poliomyelitis and the development of vaccine-derived polioviruses, especially in areas of low OPV coverage [2]. Rarely, chronic excretion of vaccine-derived viruses has been reported from persons with primary immunodeficiency disorder (PIDD), a group of inherited genetic disorders that predispose individuals to recurrent or persistent infections [2, 3]. Persons with PIDD may have long-term intestinal replication of vaccine-related
polioviruses [4–11], which over time can lead to the excretion of vaccine-derived viruses, termed immunodeficiency-associated vaccine-derived polioviruses (iVDPVs). After global polio eradication and OPV cessation, a new susceptible population might be at risk of developing paralytic polio through transmission of iVDPVs among household and community contacts of a person with PIDD who is a long-term poliovirus excreter. Long-term poliovirus excretion is defined as either prolonged (≥6 months to 5 years) or chronic (>5 years) [12].

From 1962 to 2009, 46 iVDPV infections were reported to the World Health Organization (WHO), primarily from patients with PIDD residing in middle- and high-income countries [12]. Limited data are available on the prevalence and natural history of prolonged or chronic poliovirus excretion among persons with PIDDs in low-income countries. Wild poliovirus circulation has been successfully eliminated in Bangladesh through routine OPV vaccination of infants and polio immunization campaigns, targeting children aged <5 years; however, as in other densely populated countries with a tropical climate and poor sanitation, Bangladesh remains vulnerable to iVDPV transmission, especially if OPV vaccination is stopped after certification of polio-free status. A 6-month study from February through July 2009 identified 6 laboratory-confirmed PIDD cases; 4 patients were evaluated for poliovirus excretion [13], and none were excreting poliovirus. Although it was feasible to identify children with PIDD and test them for poliovirus excretion, a sample of 4 patients was insufficient to determine whether children with PIDD could be a source of vaccine-derived polioviruses in Bangladesh. Therefore, the objective of the 2-year study from February 2011 to January 2013 was to identify infants and young children with PIDD in Bangladesh and to estimate the proportion of them who are excreting polioviruses.

METHODS

Study Sites and Population

We identified 5 hospitals for inclusion in the study: Dhaka Shishu Hospital (DSH) and the Department of Pediatrics of Bangabandhu Sheikh Mujib Medical University Hospital (BSMMU) in Dhaka; Maa O Shishu Hospital (MOSH) and the Department of Pediatrics of University of Science and Technology Hospital (USTC) in Chittagong; and Rajshahi Medical College Hospital (RMCH) was identified in Rajshahi (Figure 1).

We chose these hospitals as study sites because all 5 served as referral health centers for 3 metropolitan areas and for other areas in Bangladesh; however, BSMMU was the only medical university hospital in Bangladesh with a wide geographic catchment area. All hospitals had prior research collaboration with icddr,b.

Infants and children presenting at inpatient departments at the study hospitals who met the clinical case definition of suspected PIDD were eligible for participation in the study regardless of age; though the majority of patients were <17 years old. At each hospital, a study coordinator communicated with pediatricians to identify and report patients with suspected PIDD; patients with a diagnosis of transient immunodeficiency or a secondary immunodeficiency from human immunodeficiency virus (HIV) infection, malignancy, malnutrition, or other cause were excluded from the study.

Case Definitions

Patients suspected to have PIDD were identified according to the revised 2011 clinical criteria proposed by the Jeffrey Modell (JM) Foundation on Primary Immunodeficiency [14]; any patient presenting with ≥2 of the 10 criteria was defined as having a suspected case of PIDD. The criteria were as follows: increased frequency of common infections, including ≥4 new ear infections, ≥2 sinus infections, or ≥2 pneumonias within 1 year or recurrent abscesses; unusual infections or failure to respond to standard treatment, including ≥2 deep-seated infections, persistent thrush in the mouth or on the skin in a patient >1 year old, ≥2 mo of antibiotic treatment with little effect, and the need for intravenous antibiotics to clear infections; and other conditions suggestive of PIDD, including failure to gain weight or grow normally if <3 years of age and a family history of primary immunodeficiency. PIDD was confirmed among patients with suspected PIDD if (1) test results showed reduced quantitative immunoglobulin (QIG) titers, including immunoglobulin G, M, or A titers (IgG, IgM, or IgA), based on age-specific QIG cutoff values established for infants and children residing in Bangladesh.
Data Collection
When a suspected case of PIDD was identified and reported, the study coordinator at each hospital administered a consent form and a standardized questionnaire to collect demographic information, medical history, and clinical information. We obtained vaccination history, including the number of OPV doses received, the date of the most recent dose, and OPV vaccination history of any child <5 years of age living in the same household.

Hospital physicians collected 2 mL of blood by venipuncture from each child with suspected PIDD. Within 48 hours following collection, field staff shipped the specimen in a cold box with wet ice to the icddr,b biochemistry laboratory where serum was stored for up to 1 week at −20°C. QIG titers for IgG, IgM, and IgA were tested using the nephelometer system (Automated Chemistry Analyzer AU640; Olympus).

Each confirmed PIDD case was reported to the WHO Polio Eradication Programme in Bangladesh. A WHO surveillance medical officer then attempted to obtain 2 stool specimens (5–10 g each) ≥24 hours apart from each patient with PIDD, using an approved kit [16], and ensured that these specimens were transported according to WHO protocol to the National Polio and Measles Laboratory, Institute of Public Health, Dhaka. Stool specimens were cultured for polioviruses using specific and transgenic cell lines maintained in the laboratory. If the stool test detected poliovirus or nonpolio enterovirus, a WHO surveillance medical officer again attempted to obtain 2 stool specimens 1 month after the initial stool collection.

Analysis
All completed questionnaires and laboratory test results were forwarded to icddr,b for double entry for data consistency.

Human Subject Protection
We obtained informed written consent from study participants or their legal guardians for minors <18 years of age. An assent form was also administered for participants 8–17 years old. We provided serum QIG and stool culture results to legal guardians. The study protocol was approved by the ethical review committees of icddr,b and DSH; other hospitals deferred ethical review to these committees. The Centers for Disease Control and Prevention relied on the study approval by the icddr,b ethical review committee.

RESULTS
During the 2-year study period, 54 suspected cases of PIDD were identified from approximately 96 000 children screened at the 5 participating hospitals: 23 from BSMMU, 7 from DSH, 7 from USTC, 8 from MOSH, and 9 from RMCH. Children with suspected PIDD lived in Dhaka, Chittagong, Rajshahi, Rangpur, Barisal, and Sylhet divisions in Bangladesh (Figure 1). All patients with suspected PIDD had ≥2 of the 10 PIDD warning signs. Among all patients with suspected PIDD, predominant warning signs included the following: ≥2 episodes of pneumonias during the preceding year (46%), persistent oral thrush (50%), administration of intravenous antibiotics to treat infections (74%), and failure to grow normally (33%). Of the 54 children with suspected PIDD, 40 (74%) were male (Table 1); 20 (39%) were <1 year of age, 14 (27%) were 1–5 years of age, and 17 (33%) were 6–10 years of age. Before recruitment, 48 patients (89%) had received ≥1 OPV dose, and 40 (74%) were reported to have received ≥3 doses.

Forty (54%) of the children with suspected PIDD had normal QIG levels, and 13 (25%) had confirmed PIDD (Table 2). Of the 13 patients with confirmed PIDD, 3 had IgG, IgM, and IgA titers below age-specific reference values, 3 had IgG and IgA below age-specific reference values, 4 had IgG titers below age-specific reference values, and 3 had IgA titers below age-specific reference values. Of the 13 patients with confirmed PIDD, patients 1, 2, and 5 had recurrent bacterial infections, including recurrent lobar pneumonia, recurrent multiple skin abscess, and septicemia, as well as IgG, IgM, and IgA titers below age-specific reference values. Patients 1 and 2 had autosomal recessive agammaglobulinemia or common variable immunodeficiency (CVID). The IgG titers were above those observed for X-linked agammaglobulinemia or severe combined immunodeficiency (SCID). Patient 5 could have had transient hypogammaglobulinemia of infancy or another disorder characterized by hypogammaglobulinemia. Cases 3, 7 and 12 had recurrent pneumonia, recurrent sinusitis, chronic suppurative otitis media, persistent oral thrush or urinary tract infection, and IgA titers below age-specific reference values, due to selective IgA deficiency, which is a more common PIDD, or rarely SCID. Patients 4, 6, and 11 had recurrent pneumonia, recurrent sinusitis, chronic suppurative otitis media, large joint arthritis, recurrent skin abscess, parotid abscess and both IgG and IgA titers were below age-specific reference values, possibly due to SCID. Cases 8, 9, 10, and 13 had persistent pneumonia, skin infection, spontaneous bacterial peritonitis, urinary tract infection, septicemia, non-response to broad-spectrum antibiotic (including injectable Meropenem, injectable Vancomycin), or failure to thrive and IgG titers below age-specific reference values, possibly owing to transient IgG deficiency or SCID.

Stool specimens were collected from 11 of the 13 patients with confirmed PIDD; 1 patient was lost to follow-up owing to an incorrect residence address, and the other patient died before a stool specimen was collected. A paired stool sample collected after 126 days from the date of first hospital admission for 1 of the remaining 11 patients with confirmed PIDD tested positive...
The second paired stool sample collected 45 days after the initial stool sample collection was negative for poliovirus. The third poliovirus test 207 days after the second paired stool sample collection and the fourth test 28 days after the third paired stool sample collection were also negative for poliovirus. Another patient’s paired stool sample collected 18 days after hospital admission was positive for nonpolio enteroviruses. The second paired stool sample collected 231 days after the initial paired stool sample collection was negative for nonpolio enteroviruses. The median duration between hospital admission and the first paired stool sample for the remaining 10 patients was 72 days (range, 8–156 days). None of these patients had detectable poliovirus or nonpolio enteroviruses in their stool samples.

The duration between the receipt of last OPV dose and the first paired stool sample collection of the patient who excreted poliovirus was 34 months. None of his family members received OPV during the prior year. In the remaining 8 case patients, the mean interval between hospital admission and receipt of the last OPV dose or OPV vaccination of a household contact was 3 years (range, 3 months to 9 years). The clinical outcome in these patients with PIDD was not ascertained as part of our study.

**DISCUSSION**

We confirmed 13 PIDD cases during the 2-year study, using a standardized clinical case definition and QIG testing at 5 referral and teaching hospitals in Bangladesh. Although each patient with PIDD had received ≥1 dose of OPV 3 months to 8 years before hospital admission, stool specimens collected from 11 PIDD case patients were negative for poliovirus, suggesting that these patients were able to mount an adequate immune response to vaccination. One child was excreting poliovirus 34 months after OPV receipt; however, we were unable to determine whether there was OPV exposure after this dose or whether the detected poliovirus was divergent from the original vaccine strain. Owing to miscommunications, the poliovirus isolates from the single positive case were discarded inadvertently and therefore not available for sequencing. The second paired stool sample collected 45 days after the first paired stool sample was negative for poliovirus, suggesting that the patient was not a chronic poliovirus excreter. This patient may have been a prolonged poliovirus excreter, if we were certain that poliovirus infection acquired during the last dose of OPV. This case also may have represented community exposure to OPV in a country with

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**Table 1. Characteristics and Clinical History of Children With Suspected or Confirmed PIDD Reported in Bangladesh, February 2011 to January 2013**

<table>
<thead>
<tr>
<th>Characteristics or History</th>
<th>Suspected PIDD (n = 54)a</th>
<th>Clinically Suspected PIDD With Normal Laboratory Result (n = 41)</th>
<th>Laboratory Result Confirming PIDD (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>74 (40)</td>
<td>68 (28)</td>
<td>92 (12)</td>
</tr>
<tr>
<td>Received OPV1</td>
<td>89 (48)</td>
<td>93 (38)</td>
<td>77 (10)</td>
</tr>
<tr>
<td>Received OPV3</td>
<td>74 (40)</td>
<td>76 (31)</td>
<td>69 (9)</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 Ear infections within 1 y</td>
<td>7 (4)</td>
<td>2 (1)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>≥2 sinus infections within 1 y</td>
<td>17 (9)</td>
<td>12 (5)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>≥2 pneumonias within 1 y</td>
<td>46 (25)</td>
<td>46 (19)</td>
<td>46 (6)</td>
</tr>
<tr>
<td>Recurrent abscesses</td>
<td>28 (15)</td>
<td>27 (11)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>≥2 deep-seated infections</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Persistent oral thrush if &gt;1 y oldb</td>
<td>50 (17)</td>
<td>54 (13)</td>
<td>40 (4)</td>
</tr>
<tr>
<td>≥2 mo of antibiotic treatment</td>
<td>31 (17)</td>
<td>29 (12)</td>
<td>38 (5)</td>
</tr>
<tr>
<td>Needed intravenous antibiotics to treat infections</td>
<td>74 (40)</td>
<td>73 (30)</td>
<td>77 (10)</td>
</tr>
<tr>
<td>Failure to grow normally if &lt;3 y oldc</td>
<td>33 (17)</td>
<td>57 (16)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Family member with PIDD or death after recurring ailment</td>
<td>11 (6)</td>
<td>7 (3)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Other infections</td>
<td>44 (24)</td>
<td>44 (18)d</td>
<td>62 (8)e</td>
</tr>
</tbody>
</table>

Abbreviations: OPV1, first dose of oral poliovirus vaccine; OPV3, third dose of oral poliovirus vaccine; PIDD, primary immunodeficiency disorder.

a Approximately 96,000 children were screened.
b Twenty-four patients with clinically suspected PIDD with normal laboratory result and 10 with confirmed PIDD were >1 year old.
c Twenty-eight patients with clinically suspected PIDD with normal laboratory result and 5 with confirmed PIDD were <3 years old.
d Including lymphadenopathy, perianal infection, persistent diarrhea, meningoencephalitis, septicemia, urinary tract infection, conjunctivitis, oral ulcer, retropharyngeal abscess, umbilical sepsis, arthritis, and cystitis.
e Including arthritis, septicemia, urinary tract infection, spontaneous bacterial peritonitis, and parotitis.
frequent supplementary immunization activities. Therefore, we did not detect chronic poliovirus excretion in this study population of PIDD case patients in Bangladesh.

Findings in a few studies conducted in middle- and upper-income countries have suggested that iVDPV excretion is a rare event. In the United States, United Kingdom, Mexico, and Brazil, none of the 346 enrolled patients with PIDD tested positive for polioviruses, with the exception of a patient from Mexico with selective IgA deficiency who excreted nondivergent vaccine-related virus for roughly 6 months [17]. Similar studies in middle-income countries will typically be constrained by small sample sizes.

Table 2. Patient Characteristics, Quantitative IgG, IgM, and IgA Titers, and Stool Specimen Results in Patients With Confirmed PIDD in Bangladesh, February 2011 to January 2013

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hospitala</th>
<th>Sex</th>
<th>Age</th>
<th>Titer (Age-Specific Reference Value), g/Lb</th>
<th>Time From Receipt of Last OPV Dose to First Stool Collection, mo</th>
<th>Stool Poliovirus Culture Resultd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BSMMU</td>
<td>Male</td>
<td>7 y</td>
<td>4.04 (7.3–15.1) 0.22 (0.5–2.10) 0.20 (0.7–3.25) 34</td>
<td>Positive Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 BSMMU</td>
<td>Male</td>
<td>8 y</td>
<td>3.71 (7.3–15.1) 0.20 (0.5–2.10) 0.20 (0.7–3.25) 46</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 BSMMU</td>
<td>Male</td>
<td>7 y</td>
<td>13.9 (7.3–15.1) 0.79 (0.5–2.10) 0.70 (0.7–3.25) 32</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 BSMMU</td>
<td>Male</td>
<td>8 y</td>
<td>1.02 (7.3–15.1) 8.08 (0.5–2.10) 0.43 (0.7–3.25) 47</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 BSMMU</td>
<td>Male</td>
<td>1 y</td>
<td>0.75 (4.0–12.5) 0.20 (0.4–1.6) 0.20 (0.35–1.65) 3</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 BSMMU</td>
<td>Male</td>
<td>7 y</td>
<td>0.75 (7.3–15.1) 5.83 (0.5–2.10) 0.20 (0.7–3.25) 36</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 RMCH</td>
<td>Male</td>
<td>2 y</td>
<td>10.2 (4.0–12.5) 0.75 (0.4–1.6) 0.35 (0.35–1.65) 11</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 RMCH</td>
<td>Male</td>
<td>17 d</td>
<td>5.97 (7.5–15) 0.36 (0–0.2) &lt;0.20 (0–0.1) 17</td>
<td>Unvaccinated NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>9 RMCH</td>
<td>Male</td>
<td>18 d</td>
<td>5.59 (7.5–15) 1.34 (0–0.2) &lt;0.20 (0–0.1) 18</td>
<td>Unvaccinated NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10 RMCH</td>
<td>Male</td>
<td>2 mo</td>
<td>2.62 (2.7–7.5) 0.62 (0.12–0.87) &lt;0.20 (0.06–0.58) 20</td>
<td>Unvaccinated NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>11 DSH</td>
<td>Male</td>
<td>8 y</td>
<td>2.60 (7.3–15.1) 1.04 (0.5–2.10) 0.20 (0.7–3.25) 43</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 DSH</td>
<td>Female</td>
<td>8.5 y</td>
<td>8.65 (7.5–15.1) 1.51 (0.5–2.10) 0.58 (0.7–3.25) 45</td>
<td>Unknown NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 USTC</td>
<td>Male</td>
<td>12 y</td>
<td>2.06 (7.3–15.1) 1.61 (0.5–2.10) 2.52 (0.7–3.25) 106</td>
<td>Negative NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BSMMU, Bangabandhu Sheikh Mujib Medical University Hospital; DSH, Dhaka Shishu Hospital; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; NA, not available; NPEV, nonpolio enterovirus; OPV, oral poliovirus vaccine; PIDD, primary immunodeficiency disorder; RMCH, Rajshahi Medical College Hospital; USTC, University of Science and Technology Hospital in Chittagong.

a BSMMU and DSH are in Dhaka, USTC in Chittagong, and RMCH in Rajshahi.
b Titer below the lower limit of the age-specific quantitative immunoglobulin data from the United Kingdom [15].

c Months from receipt of last OPV dose by case patient or household contact, based on recall or the child’s vaccination card.
d Two stool specimens were collected if the result of the first specimen was positive according to World Health Organization guidelines [16].

* Stool specimens were not collected before the death of patient 8, and patient 12 was lost to follow-up (address not available).
In low-income countries where limited information was available regarding PIDD, the 10 JM Foundation warning signs [14] provided relatively sensitive criteria for identifying patients with suspected PIDD. Physicians were able to easily apply clinical criteria when enrolling patients with suspected PIDD. The WHO assessment criteria for PIDD [26], which divide patients into 7 main groups according to family history and clinical presentation, are similar to the 10 JM Foundation warning signs. In addition to performing a complete blood cell count and measuring QIG levels, WHO also recommends enumeration of a patient’s T and B cells; these investigations require a number of costly diagnostic tests that were not available for this study.

Using QIG test results to confirm the diagnosis of PIDD has a limitation; patients with PIDD without B-cell deficiencies, approximately 30% of PIDD case patients, were not identified [27, 28]. In the WHO iVDPV registry, 32 patients (70%) with PIDD case patients at risk for chronic poliovirus excretion. PIDD had B-cell deficiencies; patients with PIDD without B-cell deficiencies, ap-

The study group chose age-specific QIG cutoff levels for PIDD based on the 2.5th percentile value for healthy children from the UK [15]. The 2.5th percentile QIG values were significantly higher among rural Bangladeshi school children aged 5–7 years [29] than the values we used in this study. Therefore, if lower limits of normal age-specific QIG levels are higher in Bangladesh than in the United Kingdom, the number of confirmed PIDD cases in this study is probably underestimated. Research is warranted to develop age-specific normal QIG levels appropriate for Bangladesh.

Our study demonstrated that, at selected referral hospitals using few resources, the risk of chronic excretion of poliovirus among PIDD case patients is probably low. However, owing to sample size limitations, we recommend expanding the scope and intensity of surveillance activities at additional referral hospitals in other areas of the country. One strategy would be to incorporate strategies for PIDD case detection into the country’s acute flaccid paralysis surveillance system. Clinical and laboratory training for physicians and immunologists is also needed. Enhanced collaboration between regional reference laboratories and the national laboratory will be crucial to ensure sequencing of poliovirus isolates from patients with PIDD. These efforts will be essential for further case detection, better understanding of the risk of iVDPV excretion, and development of effective prevention and control strategies after OPV cessation, especially for densely populated and tropical countries such as Bangladesh, where even a minimal risk could have devastating public health consequences.

Notes

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