MAJOR ARTICLE

Poliovirus Vaccine Shedding among Persons with HIV in Abidjan, Cote d'Ivoire

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(See the editorial commentary by Hull and Minor and the article by Laassri et al., on pages 2033–5 and 2092–8, respectively.)

Background. As polio eradication nears, the development of immunization policies for an era without the disease has become increasingly important. Outbreaks due to circulating vaccine-derived poliovirus (VDPV) and rare cases of immunodeficient persons with prolonged VDPV shedding lend to the growing consensus that oral poliovirus vaccine (OPV) use should be discontinued as soon after polio eradication as possible. The present study was conducted to assess whether persons infected with human immunodeficiency virus (HIV) experience prolonged VDPV shedding and serve as a source of reintroduction of virus into the population.

Methods. Adults infected with HIV had specimens tested (1) 8 months after a mass OPV campaign, to determine whether poliovirus related to OPV administered during the campaign was present (i.e., prolonged excretion), and (2) starting 7 weeks after a subsequent campaign, to determine whether poliovirus could be detected after the height of OPV exposure.

Results. A total of 419 participants were enrolled—315 during the 8–12 months after an OPV campaign held in 2001 and 104 during the 7–13 weeks after a 2002 campaign. No poliovirus was isolated from any participants.

Conclusions. It appears unlikely that adults infected with HIV experience prolonged vaccine virus shedding, and, therefore, they probably represent a minimal risk of reintroducing vaccine virus into the population after poliovirus has been eradicated.

Since adopting the initiative to eradicate polio globally in 1988, 3 World Health Organization regions (American, Western Pacific, and European) have been certified as polio free, and the number of polio-endemic countries has decreased from 125 in 1988 to 6 in 2003 [1, 2]. As a polio-free world approaches, developing polio immunization policies after eradication has become increasingly relevant, especially in light of risks associated with the use of oral poliovirus vaccine (OPV). In addition to vaccine-associated paralytic polio (VAPP), there are risks of circulating vaccine-derived poliovirus (cVDPV), which can maintain person-to-person transmission and cause paralytic disease, and immunodeficiency-related VDPV (iVDPV), which is associated with prolonged infection and shedding of mutant poliovirus vaccine strains among persons with primary immune deficiencies. The polio eradication program depends on OPV to interrupt the final chains of poliovirus transmission; however, these discoveries lend to the growing consensus that OPV use should be discontinued as soon after polio eradication as possible. Much work is under way to develop a safe and efficient approach for accomplishing this objective globally.

Genetically, VDPVs are defined as having >1% sequence difference from the Sabin vaccine virus [3]. The first polio outbreak caused by cVDPVs was detected on the island of Hispaniola in 2000; it resulted in the paralysis of 21 children and clearly demonstrated for the first time the potential for vaccine strains to circulate and cause paralytic disease [4]. Subsequent cVDPV outbreaks were detected in the Philippines in 2001 (3 cases),

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Madagascar in 2002 (4 cases), and, through retrospective analysis, Egypt in 1988–1993 (30 cases) [5–7]. Absence of wild poliovirus of the same serotype and low vaccination coverage were associated with the outbreaks; however, it is not clear whether low population immunity alone is sufficient for the emergence of cVDPVs [8]. A complementary explanation is that only after essential mutations for virulence and transmissibility are acquired within an individual (i.e., an immunodeficient individual) are vaccine viruses able to circulate and cause disease in the population.

Shedding of iVDPVs for a duration of at least 6 months has been identified in 19 patients with B cell immune deficiency disorders from 7 different countries [9–17]. Some of these patients have shed virus for >10 years, and some have developed paralytic polio, demonstrating that prolonged replication even within a single individual increases the virulence of these vaccine-related viruses. There has been no evidence of paralytic disease resulting from secondary exposure to iVDPVs; however, since most contacts of these individuals are immune, the significance of this observation is uncertain. Studies designed to search for more patients with prolonged shedding of vaccine virus show that these cases are rare [16, 18]. One study has reported that a healthy child possibly shed vaccine virus for 6 months; however, this finding is not definitive, because serial sampling did not cover the entire 6-month period, and the child's mother was HIV infected [19].

VAPP is the rare occurrence of paralytic polio among OPV recipients or contacts of recipients, which occurs an estimated rate of 1 case per every 2 million OPV doses administered. VAPP differs from VDPV in that the virus is highly related to virus found in the vaccine (>99.5% sequence identity). Patients with B cell immune disorders are at increased risk for VAPP [20]. VAPP does not appear to be associated with HIV infection, since there has been only 1 report of such a case, despite widespread use of OPV and the subsequent successful elimination of indigenous wild poliovirus in areas with high HIV prevalence, such as those in several southern African countries [21].

There is no evidence to date indicating that immune deficiency caused by HIV is associated with VDPVs; however, few studies have been conducted to directly measure this association. One study on the shedding of vaccine virus among adults with HIV in Guatemala has preliminarily found no poliovirus shedding among 101 subjects (N. Halsey, personal communication). Given the geographic foci of high HIV prevalence in several OPV-using countries, a small increase in duration of viral shedding of several weeks to months may enhance the evolution and spread of vaccine viruses. Therefore, a large study in a high-risk setting in terms of HIV prevalence, OPV exposure, and conditions that facilitate vaccine virus spread (e.g., low vaccination coverage, high population density, poor hygiene, and tropical climate) was needed to evaluate the risk of persistence of vaccine virus shedding among persons with HIV infection.

Cote d'Ivoire represents a potentially high-risk setting for poliovirus vaccine exposure and spread. In terms of OPV exposure opportunity, the country uses OPV as part of routine and supplementary immunization. Nationwide, ~2.5 million children aged <5 years have been vaccinated with OPV during each of 2 rounds (3–5 days each) held in the autumn of each year during 1996–2002. The large quantities of OPV administered during mass campaigns over short time periods result in intense vaccine virus excretion and circulation during the weeks after the campaign [22]. In terms of vaccine spread, Cote d'Ivoire has high population density in urban areas, as well as substantial immunity gaps; reported routine immunization coverage for 3 doses of OPV was 54% in 2002. Although adults do not receive vaccine during mass campaigns, they can be infected secondarily by vaccine virus excreted by a vaccinated child [23]. The prevalence of HIV in Cote d'Ivoire was estimated by United Nations AIDS (UNAIDS) to be 7% in 2002. To investigate the possibility of long-term shedding of vaccine virus among persons infected with HIV, in the present study we enrolled persons attending an HIV clinic and tested fecal specimens to determine whether participants had been secondarily exposed to and continued to shed virus related to OPV administered during a mass immunization campaign held 8 months earlier.

PARTICIPANTS AND METHODS

Study design and enrollment. Poliovirus testing was conducted on stool specimens collected from adults with HIV infection during 2 phases: (1) starting 8 months after a mass OPV campaign held in the autumn of 2001, to determine whether any persons were shedding poliovirus with genetic evidence of having originated at the time of the mass campaign (i.e., prolonged excretion), and (2) starting 7 weeks after the autumn 2002 OPV campaign, to determine whether poliovirus could be detected among this patient population after the height of OPV exposure opportunity. Participants were selected from among patients seeking care at 3 Drug Access Initiative (DAI) clinics in Abidjan. The DAI is a Ministry of Public Health and UNAIDS program to provide subsidized antiretroviral therapy. Data collected as part of routine initial DAI visits include results from a medical evaluation, HIV test results, CD4 cell count measurements, and responses to questions related to behavior and socioeconomic status. Eligible patients included all DAI patients who were aged ⩾18 years and who had not received antiretroviral therapy during the previous 6 months.

Federal guidelines for human subject research were followed in the present study. If patients agreed to participate, written consent was obtained, and a stool specimen was collected. Diarrhea has been known to inhibit poliovirus replication in the

Table 1. Patient characteristics and variables related to oral poliovirus vaccine exposure opportunity.

Characteristic	Participants, no. (%)[a]
Age, years	
18–25	52 (13)
26–35	169 (40)
36–45	135 (32)
46–55	54 (13)
56–65	9 (2)
Female sex	249 (59)
CD4 cell count at time of stool collection, cells/mm^3	
<50	84 (20)
50–199	140 (33)
200–499	143 (34)
⩾500	39 (10)
Children aged <15 years in household, no.	
None	292 (70)
1–3	77 (18)
⩾4	49 (12)
Type of household	
Slum or communal living	235 (56)
Apartment or house	162 (39)
Other	21 (5)

[a] Data are for patients in both study phases (n = 419); there were no statistical differences between phase 1 and phase 2. Data on CD4 cell count at time of stool collection were missing for 13 patients, data on no. children aged <15 years in household were missing for 1 patient, and data on household type were missing for 1 patient.

intestinal tract; therefore, physicians noted whether patients had febrile diarrhea, defined as >3 loose stools/day in the presence of concurrent fever (temperature, >38°C), before providing the specimen. Patients were given the option of providing a specimen on the same day or returning the next day with a specimen. Stool specimens were collected in standard specimen collection kits and immediately placed in ice boxes. At the end of each day, specimens were collected from all clinics and transferred to the Projet Retrovirus–Cote d'Ivoire (Retro-CI) laboratory for aliquoting and testing.

Specimen processing. Serologic tests for HIV status and CD4 cell count measurements were conducted at the Projet Retro-CI, a collaborative project between the Ministry of Health, Cote d'Ivoire, and the US Centers for Disease Control and Prevention (CDC). Stool specimens were examined for the presence of poliovirus; nonpolio enteroviruses (NPEVs), to serve as an indicator for laboratory quality and maintenance of the cold chain; and specified parasites, to provide diagnosis and treatment options. Specimens underwent poliovirus isolation testing by cell culture in 2 laboratories; 1 aliquot was kept at 4°C and transported on the same day to the Institute Pasteur, Adiopoudome, Cote d'Ivoire, and another was stored at −20°C and shipped on dry ice in 2 shipments to the CDC enterovirus laboratory [24].

Definition of prolonged excretion. Any poliovirus isolates were to undergo molecular sequencing of the VP1 region at the CDC, to determine their genetic relatedness to Sabin reference strains. The VP1 region of poliovirus mutates at a rate of ~1% nucleotide substitutions/year; therefore, prolonged shedding in this study was defined as having >0.5% nucleotide substitutions in the VP1 region. This number of mutations could suggest recent virus infection; for example, a person shedding virus from a recent exposure to vaccine from ongoing routine vaccination would have virus that looked similar to the Sabin vaccine (<0.5% mutations). To establish whether prolonged shedding was occurring among the individuals identified, further serial specimen collection and testing would be sought.

Statistical analysis. The sample size was based on having 80% power to detect at least a 1% shedding rate with 95% confidence. The following formula based on exact methods for a binomial distribution was used to calculate sample size and confidence bounds around the point estimate, $\Phi = 1 - (1 - \alpha)1/n$, where Φ is the upper limit for the proportion of shedding, α is the level of confidence in which the level of shedding is $<\Phi$, and n is the sample size. Data were analyzed using Epi Info [25], and statistical comparisons were made using χ^2 tests.

RESULTS

Patient enrollment. During July–October 2002, 315 patients were enrolled as part of the first phase of the study, 8–12 months after the autumn 2002 mass OPV campaign. During December 2002–January 2003, 104 patients were enrolled as part of the second phase of the study, 7–13 weeks after the first round of the mass OPV campaign held in December 2002.

Patient characteristics. There were no statistical differences in age, sex, CD4 cell count, number of children aged <15 years in the household, and household type when patients from the 2 phases were compared; therefore, summary data are aggregated from this point onward. The majority of patients (72%) were aged 26–45 years, and 59% were female (table 1). Fifty-three percent of patients had CD4 cell counts <200 cells/mm^3, 34% had CD4 cell counts 200–499 cells/mm^3, and 10% had CD4

Table 2. Poliovirus and nonpolio enterovirus isolation results.

Laboratory test, phase	Participants shedding, no. (% [95% CI])
Poliovirus isolation	
Phase 1 (n = 315)	0 (0 [0–0.95])
Phase 2 (n = 104)	0 (0 [0–2.02])
Overall (n = 419)	0 (0 [0–0.71])
Nonpolio enterovirus isolation	
Phase 1 (n = 315)	8 (2.5 [NA])
Phase 2 (n = 104)	4 (3.8 [NA])
Overall (n = 419)	12 (2.9 [NA])

NOTE. CI, confidence interval; NA, not applicable.

[a] Based on exact methods.

cell counts ⩾500 cells/mm^3. Thirty-one (7.4%) of the patients had febrile diarrhea.

Laboratory results. No polioviruses were detected during either phase or from either laboratory (table 2). The 95% confidence interval (CI) of the probability of finding 0% of study participants shedding vaccine virus 8 months after a mass OPV campaign was 0%–0.95%. If the sample sizes for both of the phases are combined, the upper bound of the 95% CI around the shedding proportion decreases to 0.71%.

The NPEV isolation rates were 2.5% (8 isolates from 315 specimens) and 3.8% (4 isolates from 104 specimens) among phase 1 and phase 2 participants, respectively. Nonpolio enteroviruses were detected from patients throughout each month of the study; the monthly NPEV isolation rate ranged from 1.5% to 10%.

Socioeconomic variables related to OPV exposure opportunity. Most participants (70%) reported having no children in the household; however, 56% of patients reported living in a slum or communal living situation, which is likely to involve close contact with young children (table 1).

DISCUSSION

Data from this study suggest that it is very likely that <1% of adults with HIV are shedding poliovirus. This low prevalence suggests minimal risk of this population being a source of reintroduction of vaccine-related virus into a population after wild poliovirus has been eradicated. Results from a study of this size suggest that, if prolonged shedding occurs, the prevalence is low. The study's sensitivity to detect virus if it was present, as measured by the consistent NPEV isolation rates, indicates that, if study participants were shedding poliovirus, it is likely that it would have been detected. These results are reassuring for countries that have a high HIV prevalence and administer large quantities of OPV annually through routine childhood vaccinations and mass vaccination campaigns.

The typical poliovirus shedding period occurs ~1–4 weeks after vaccination of primary recipients [23]. A civil conflict prohibited enrollment of participants immediately after the campaign, during the most likely shedding period for familial or extrafamilial contacts; therefore, the absence of poliovirus in study participants 7–13 weeks after the mass campaign was not entirely unexpected. Other analyses of data from India and Cuba showed that poliovirus vaccine detection rates after mass OPV campaigns returned to baseline rates within 5 weeks of the campaigns.

Another interpretation of the lack of poliovirus vaccine detection among participants from either phase of the study could be that they were not exposed to OPV. The participant's extent of contact with children vaccinated during the campaign was not directly measured. Only a small proportion of study participants (12%) had at least 1 child aged <15 years in their household; however, given the large quantities of OPV that were introduced into the population and the high frequency of slum or communal living, the opportunity for exposure was likely to be substantial.

If persons with HIV were to experience prolonged shedding of vaccine virus, it would most likely occur during advanced disease, when susceptibility to a variety of infectious agents is increased and when secondary suppression of humoral immunity is most likely to occur [26]. Only 53% of the study population were severely immune compromised (<200 CD4 cells/mm^3). Recalculating the confidence bounds to include only the subset of severely immune compromised patients from the first phase of the study ($n = 170$) increases the upper bound of the 95% CI of the shedding proportion to 1.75%.

The present study was conducted among adults with HIV, because of the significant proportion of individuals with immune deficiencies they represent in the world and the potential risk posed if prolonged shedding did occur. Children with HIV, however, have characteristics more consistent with potential long-term excretion of vaccine-related virus. These characteristics include having immature immune systems, being susceptible to poliovirus infection, and being likely to be exposed to OPV through direct or indirect vaccination. A recent study on vaccine virus persistence among children with HIV in Kenya has preliminarily found no difference in the duration of excretion of vaccine virus between HIV-positive and -negative groups (N. Khetsuriani, personal communication). Further research in the area of prolonged carriage of vaccine virus should focus on children with HIV.

Sutter et al. described key routine vaccination policy options to consider for the posteradication era and summarized key remaining gaps in scientific knowledge [27]. A major consideration is the potential for long-term carriers of poliovirus vaccine to reseed the world with virus that could cause paralytic disease or outbreaks. The present study provides data indicating that the rare chronic shedding of vaccine virus associated with primary immune deficiencies has not been observed with immunodeficiency caused by HIV infection. This will provide a measure of reassurance for countries with high HIV prevalence and for global policy makers as they consider recommendations on how to address the risk for introduction of polio vaccine virus after polio eradication has been achieved.

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