SUPPLEMENT ARTICLE

Switch From Oral to Inactivated Poliovirus Vaccine in Yogyakarta Province, Indonesia: Summary of Coverage, Immunity, and Environmental Surveillance

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Background. Inactivated poliovirus vaccine (IPV) is rarely used in tropical developing countries. To generate additional scientific information, especially on the possible emergence of vaccine-derived polioviruses (VDPVs) in an IPV-only environment, we initiated an IPV introduction project in Yogyakarta, an Indonesian province. In this report, we present the coverage, immunity, and VDPV surveillance results.

Methods. In Yogyakarta, we established environmental surveillance starting in 2004; and conducted routine immunization coverage and seroprevalence surveys before and after a September 2007 switch from oral poliovirus vaccine (OPV) to IPV, using standard coverage and serosurvey methods. Rates and types of polioviruses found in sewage samples were analyzed, and all poliovirus isolates after the switch were sequenced.

Results. Vaccination coverage (>95%) and immunity (approximately 100%) did not change substantially before and after the IPV switch. No VDPVs were detected. Before the switch, 58% of environmental samples contained Sabin poliovirus; starting 6 weeks after the switch, Sabin polioviruses were rarely isolated, and if they were, genetic sequencing suggested recent introductions.

Conclusions. This project demonstrated that under almost ideal conditions (good hygiene, maintenance of universally high IPV coverage, and corresponding high immunity against polioviruses), no emergence and circulation of VDPV could be detected in a tropical developing country setting.

Keywords. polio; immunization; poliovirus circulation.

Cases of paralysis caused by poliovirus have decreased by >99% since the World Health Assembly's resolution to eradicate polio in 1988. In 2012, a total of 223 cases of poliomyelitis caused by wild polioviruses were reported worldwide from 4 countries—the lowest number ever recorded in history [1].

Polio eradication requires not only complete absence of circulating wild polioviruses but also absence of vaccine polioviruses contained in widely used oral poliovirus vaccine (OPV). OPV needs to be withdrawn because in rare circumstances vaccine poliovirus may revert back to assume the neurovirulence and transmission characteristics of wild poliovirus and may establish community circulation causing outbreaks of paralytic disease, referred to as vaccine-derived poliovirus (VDPV) outbreaks [2, 3]. In 2012, 30% of reported paralyses caused by polioviruses were due to VDPVs [1], and this proportion is likely to further increase as wild poliovirus eradication nears while OPV continues to be used. Paralysis caused by wild poliovirus is clinically indistinguishable from paralysis caused by VDPV [4].

Three serotypes of poliovirus have been described (types 1, 2, and 3). Wild poliovirus type 2 has been

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eliminated in 1999 [5], but outbreaks caused by type 2 VDPV represent the vast majority of all VDPV outbreaks and also the vast majority of paralytic cases caused by VDPVs [1].

To achieve elimination of vaccine polioviruses from the community, OPV use in routine and campaign immunizations must stop while population immunity to polioviruses must be maintained at high level. The withdrawal of OPV is planned in a phased manner. The Global Polio Eradication Initiative envisions that in 2016 trivalent OPV will be replaced by bivalent OPV 1 and 3, in a synchronized manner worldwide, followed by complete OPV cessation several years later.

Following recommendation of the Strategic Advisory Group of Experts (SAGE) of the World Health Organization from 2012, ≥1 dose of inactivated poliovirus vaccine (IPV) will be added to the routine immunization schedule in all OPV-using countries before the switch from trivalent to bivalent OPV to maintain population immunity against type 2 VDPV. There is no risk of VDPVs emerging from IPV [2, 3, 6].

The Yogyakarta IPV Demonstration Project was designed to provide operational and scientific data in connection with complete switch from OPV to IPV [7]. The key objectives of the project were to determine whether the switch to IPV provided comparable coverage and immunity protection against all 3 poliovirus serotypes, to verify that OPV virus disappeared from the environment after cessation of OPV use, and to demonstrate that no VDPVs emerged after the switch to IPV.

Yogyakarta Province was selected as a site of the Demonstration Project because of its well-functioning public health service, including childhood immunizations reaching high coverage for all antigens; its centralized sewage system enabling environmental surveillance; and its tropical climate, providing conditions that would be similar to those in other developing countries. The population of Yogyakarta Province is estimated at 3 million, with approximately 50 000 children born every year; it is divided into 4 districts and 1 municipality.

OPV was withdrawn from use and replaced by IPV in Yogyakarta on 3 September 2007, in a synchronized manner involving both government and private health facilities. Before the switch, OPV in Yogyakarta was administered at birth and at 2, 3, and 4 months of age. Since the switch, IPV has been given at 2, 3, 4, and 9 months of age.

This article summarizes data obtained between 2004 and 2012 from environmental surveillance for polioviruses as well as from pre- and post-switch serological and vaccination coverage surveys. We also discuss findings from the evaluation of programmatic impact of the vaccine switch which was carried out in February 2008.

METHODS

Coverage Surveys

Two independent coverage surveys were carried out by Gadjah Mada University, Yogyakarta, one before the switch, in July and August 2004 and one after the switch, in September 2010. A standard 30-by-7 cluster sampling method was used to estimate the coverage in urban (Yogyakarta City) and rural (the remaining 4 districts) areas of Yogyakarta Province [8]. In this 2-stage sampling process, 30 localities (clusters) in Yogyakarta City and 30 villages (clusters) in the province's 4 rural districts were selected.

In the second stage, 7 children between 1 and 2 years of age were randomly selected in each cluster to obtain a sample of 420 children in each survey. A questionnaire was used to acquire information from caregivers on vaccination status, dates and location of vaccination, and the mother's knowledge of and attitude toward polio vaccinations. The dates of vaccinations were copied from vaccination records when available; otherwise, the information provided by caregivers was noted. The primary objective of the coverage surveys was to describe difference in vaccination coverage before and after the vaccine switch [9].

Serological Surveys

Two serological surveys were conducted in Yogyakarta by the Indonesian Ministry of Health, the first before the vaccine switch in December 2005 and the second after the switch between August and December 2011. In 2005, 1 blood sample was collected by venipuncture when infants who received 4 doses of OPV were presented for routine measles vaccination at approximately 9–11 months of age (blood was collected before the measles vaccine administration).

In 2011, 2 blood samples were collected by venipuncture. The first sample was obtained when infants who received 3 IPV doses were presented for measles vaccination and the fourth IPV dose at approximately 9 months of age. The second sample was obtained 30 days after the first sample.

In both surveys, subjects were selected from 10 health centers (8 in rural Yogyakarta Province and 2 in urban Yogyakarta). From each health center, 30 or 20 subjects, respectively, were selected at random in 2005 and 2011 to obtain a total of 300 children in 2005 and 200 children in 2011 surveys.

Serum samples from the first survey were tested for polio antibodies by neutralization assays conducted in parallel at the national polio laboratory network of Jakarta and at the United States Centers for Disease Control and Prevention in Atlanta following standard protocols [10]. Serum samples from the second survey were processed only at the national polio network laboratory in Jakarta. The methods used in both laboratories were very similar, except that the laboratory in Jakarta diluted out to 256 (and not 1024). Seropositivity was defined as presence of neutralizing antibody titers ≥1:8.

The primary objective of the serological surveys was to demonstrate that humoral immunity to polio is not affected by switching from oral to injectable poliovirus vaccine. In 2011, an additional objective was to quantify the added immunological value of the fourth dose of IPV.

Environmental Surveillance for Polioviruses

Sewage samples were collected from an inlet into the waste water treatment plant in Bantul (IPAL Sewon Bantul) serving a subset of urban Yogyakarta since July 2004. They were collected by the Environmental Health Department and Provincial Health Laboratory of Yogyakarta using a grab method, once a week between July 2004 and December 2007 and twice a week since January 2008. Sample collection was discontinued on several occasions (February–March 2007, February–March 2009, July 2009–September 2010, January–July 2011, September–October 2012) for a variety of reasons, including natural disasters (earthquakes, volcanic eruptions) and delays in funding.

Samples were sent to National Polio Laboratory at Biofarma, Bandung, Indonesia, for processing and identification of polioviruses. Each 1-L sample of waste water was divided into 2 aliquots; one was further processed using a 2-phase separation method and inoculated into L20B and RD cell lines that were used for isolation [11], while the other was kept as a backup. Samples found to be positive for polioviruses were sequenced in National Polio Laboratory Biofarma, Bandung, Indonesia, and in THL Laboratory, Helsinki, Finland.

The primary objective of the environmental sampling was to document emergence of circulating VDPVs in Yogyakarta. The secondary objective was to describe the circulation of vaccine-related polioviruses in the environment before and after the switch.

RESULTS

Coverage Surveys

In 2004, vaccination coverage information from 420 eligible children was obtained (210 from urban Yogyakarta and 210 from rural districts); in 2010, the same information was obtained from 426 eligible children (215 from urban Yogyakarta and 211 from rural districts).

In both 2004 and 2010, the vaccination coverage was >95% for all antigens, in both urban and rural parts of the province. No difference in coverage was detected between 2004 and 2010 (Table 1). The mean age for receiving OPV 4 in 2004 was 4.8 months; in 2010 it was 4.8 months for IPV 3 and 9.5 months for IPV 4 [9, 12].

Serological Surveys

In the 2005 survey of the 292 infants enrolled, 99% had a history of receiving 3 doses of OPV (290 of 292) and 97% received a fourth OPV dose (284 of 292). Only 3 infants received a fifth dose of OPV; and these infants were excluded from the analysis. Thus, the final study population was restricted to the 284 infants with a history of having received 4 doses of OPV. Seroprevalence levels (defined as ≥1:8) among 9–11-month-old infants were 98.6% against poliovirus type 1, 99.3% against poliovirus type 2, and 98.2% against poliovirus type 3. The overall median titers were 1287 for type 1, 1152 for type 2, and 724 for type 3.

Table 1. Vaccination Coverage Survey Results, Yogyakarta Province, 2004 and 2010

	Yogyakarta City Coverage, %		Rural District Coverage, %	
Immunization	2004	2010	2004	2010
Hepatitis 0[a]	100	98.1	99.5	99.5
BCG	99	100	99.5	99.5
DPT 1	100	100	99.5	100
DPT 2	100	99.5	99.5	100
DPT 3	100	100	99.5	99.1
Polio 0[b]	100		99.5	
Polio 1	100	100	99.5	100
Polio 2	99.5	99.5	99.5	100
Polio 3	98.6	99.5	99.5	99.1
Polio 4	. . .	99.5	. . .	97.2
Measles	98.1	99.5	99.5	97.6

Abbreviation: DPT, diphtheria-pertussis-tetanus.

[a] Hepatitis 0 in the 2010 survey was comparable to hepatitis 1 in the 2004 survey.

[b] In the 2004 survey, polio 0 represents oral poliovirus vaccine given soon after birth. In the 2010 survey, polio 4 represents inactivated poliovirus vaccine given at age 9 months, simultaneously with measles vaccine.

In 2011, blood samples were obtained from 188 of 200 enrolled infants aged 9 months (94%) after they had received 3 IPV doses, and a second sample was obtained from 187 of 188 infants aged 10 months (99%) after they received the fourth dose. Seroprevalence levels (defined as ≥1:8) were 100% against all 3 poliovirus types after 3 IPV doses and remained unchanged at 100% against all 3 types after the fourth IPV dose. The overall median titers were ≥256 against poliovirus types 1, 2, and 3 after 3 and 4 doses of IPV.

Environmental Surveillance

Between July 2004 and December 2012, a total of 412 sewage samples from Yogyakarta were tested for presence of polioviruses (Table 2). Vaccine poliovirus was detected in 94 of 412

Table 2. Laboratory Results, Environmental Surveillance, Yogyakarta, July 2004 to December 2012

	Sewage Samples, No. (%)	
Surveillance Results	Before OPV to IPV Switch	After OPV to IPV Switch
Sewage samples collected	137	275
Nonpolio enterovirus isolated	64 (47)	159 (58)
Vaccine poliovirus isolated	79 (58)	15 (5)
Vaccine-derived poliovirus isolated	0	0

Abbreviations: IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine.

samples (23%); most positive samples (79 of 94 [84%]) were collected before the vaccine switch, and 15 samples yielded poliovirus after the switch. Most of the detected vaccine polioviruses were type 2 (60%), followed by type 3 (31%) and type 1 (9%). No VDPVs (defined as polioviruses with ≥6 nucleotide changes from the parental Sabin strains for type 2 and ≥10 nucleotide changes for types 1 and 3) were detected using sequencing [3]. The largest number of mutations found was 4.

The nonpolio enterovirus detection rate remained stable before and after the switch, and the vaccine poliovirus detection rate dropped to zero within 3 weeks after the switch, with the exception of several single detections of vaccine polioviruses in the period since October 2007 (Figure 1).

DISCUSSION

The IPV Introduction Project in Yogyakarta demonstrated that vaccine poliovirus disappeared rapidly from the tropical developing country environment after OPV cessation. Several polioviruses isolated after the switch were likely due to importations from neighboring provinces that continued to use OPV. There has not been any evidence suggesting that vaccine polioviruses circulated for a prolonged period of time in the environment: no VDPVs were isolated from the sewage samples or from acute flaccid paralysis surveillance at any point of the project.

Similarly to IPV introduction in industrialized countries, such as New Zealand [13], Australia [14] and others [15–17], vaccine poliovirus disappeared rapidly in sewage samples. Thus, under almost ideal conditions, good hygiene, nearly universal vaccination coverage, and high population immunity, the tropical developing environment did not support the emergence and circulation of VDPV during the 5-year period after IPV introduction. It should not be automatically assumed that VDPVs will not emerge and circulate under less ideal circumstances, such as lower immunization coverage and poor hygiene. This study reinforces the requirement to achieve high immunization coverage and population immunity when OPV is discontinued.

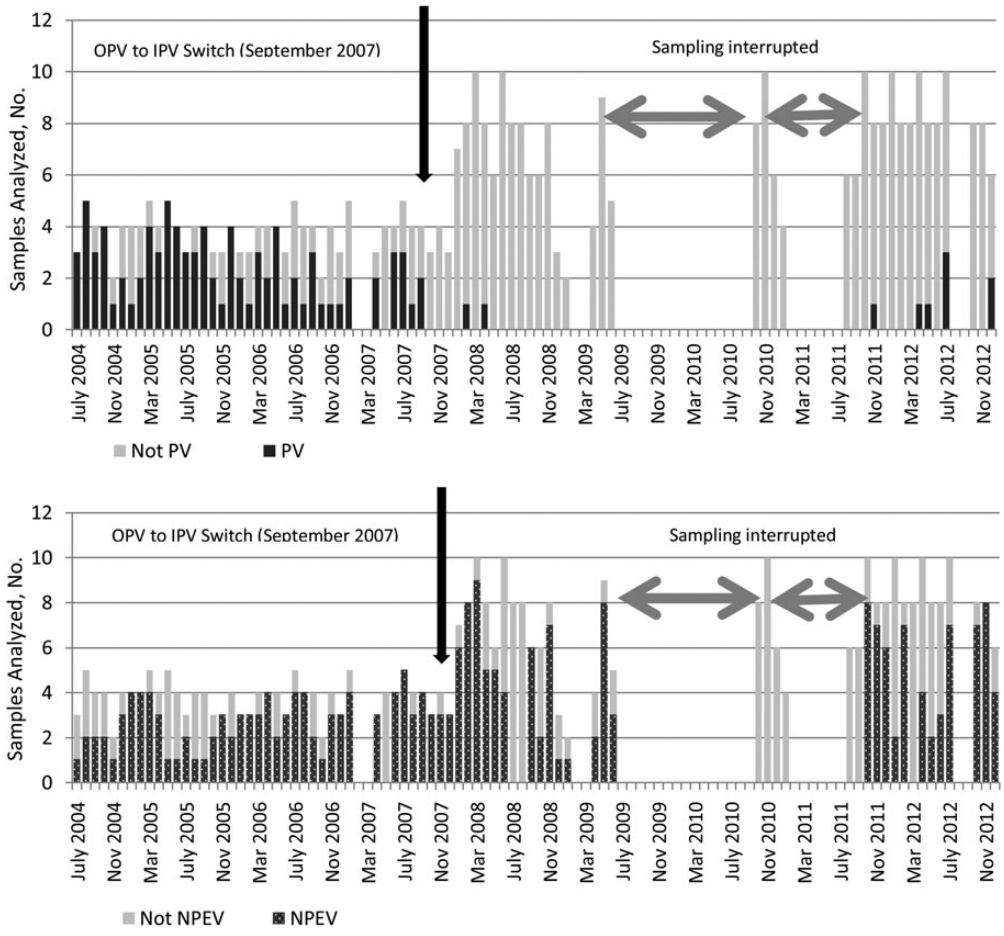

Figure 1. Poliovirus and nonpolio enterovirus (NPEV) isolations, Environmental Surveillance, Yogyakarta, July 2004–December 2012. Abbreviations: IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine.

Vaccination coverage was unchanged after the switch, suggesting that programmatically there were no significant problems with rapid introduction of IPV into the routine immunization schedule. The independent evaluation of programmatic aspects of the switch concluded that 6 months after the vaccine switch, the introduction of IPV as the only polio vaccine has been successfully achieved in Yogyakarta. The evaluation found strong evidence that administration of OPV has completely stopped and that all OPV stocks have been withdrawn. The evaluation team determined that, in all immunization clinics visited (both governmental and private), immunization against polio was being maintained at a high level. Knowledge of the IPV immunization schedule was found to be high and IPV was being correctly stored and handled. The most important programmatic challenge noted during the evaluation was initial reluctance among both parents and health workers to administer 2 injections during the same health facility visit, which may have led to delays in immunization schedule, however, these delays were not observed during vaccination coverage survey in 2010.

Seroprevalence of poliovirus neutralizing antibodies after 3 doses of IPV reached 100%. The fourth IPV dose further increased the titer; however, there is no programmatic reason to keep vaccinating children at 9 months with IPV, and this dose has therefore been removed from the immunization schedule as of 2013.

Our project had limitations. Given its length, we experienced several periods during which environmental sample collection had to be discontinued owing to natural calamities, delays in funding, or other reasons. Nevertheless, we believe that the environmental data are sufficiently robust to draw inferences. In addition, the methods were not identical between the first seroprevalence and the second seroprevalence/seroconversion study. In the first study, the samples were tested in parallel in Indonesia and at the Centers for Disease Control and Prevention, yielding similar results, whereas the testing of the second seroprevalence/seroconversion study took place only in Indonesia. Although the different testing sites are unlikely to affect the overall interpretation of the results, they preclude a more detailed analysis of the actual titer, because the cutoff dilution used in the laboratory in Indonesia was 256 instead of 1024.

The IPV Project in Yogyakarta demonstrated the programmatic feasibility of a synchronized switch from OPV to IPV. It also provided immunological evidence that protection against all types of polioviruses remains high after switch from OPV to IPV. After completion of the 5-year introduction project, the government of Indonesia decided to continue with an all-IPV schedule in the province, and environmental surveillance is also continuing.

Our analyses further suggest, that under optimal conditions in tropical developing country settings, the immunity induced by IPV is also sufficiently robust to prevent the emergence and circulation of VDPVs (even in a setting where OPV viruses are frequently introduced from travelers, visitors, or tourists from the OPV-using provinces in Indonesia). The Global Polio Eradication Initiative should build on the lessons learned from this project when implementing withdrawal of OPV and introduction of IPV into routine immunization schedules worldwide.

Notes

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