Immunogenicity of Two-Dose Booster Immunization with Conventional Inactivated Polio Vaccine in Japanese Adults

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Abstract

Background: Most Japanese adults have been vaccinated twice in childhood with the Sabin oral polio vaccine as part of routine immunization schedules. Booster vaccination is recommended for Japanese travelers to polio-endemic or high-risk countries. This study assessed the immunogenicity of a two-dose booster regimen of conventional inactivated polio vaccine (cIPV) in Japanese adults.

Methods: Healthy Japanese adults aged 20 years or older received two doses of standalone cIPV derived from virulent strains (Imovax Polio®). Serum samples were obtained before the booster vaccination and 4–6 weeks after each vaccination. Immunogenicity was evaluated by measuring serum neutralization titers against type 1, 2, and 3 poliovirus strains using a microneutralization assay.

Results: The subjects were 61 healthy Japanese adults (26 men and 35 women) with mean ± standard deviation age of 35.8 ± 8.0 years. The seropositivity rates (i.e., percentage of subjects with anti-polio antibody titers ≥1:8) before booster vaccination were 88.5%, 95.1%, and 52.5% for Sabin strains (type 1, 2, and 3, respectively); 72.1%, 93.4%, and 31.1% for virulent poliovirus strains (type1: Mahoney strain; type 2: MEF-1 strain; and type 3: Saukett strain, respectively); and 93.4%, 93.4%, 93.4% and 88.5% for type 2 vaccine-derived poliovirus strains (SV3128, SV3130, 11196, and 11198, respectively). After one dose of cIPV, all seropositivity rates increased to 98.4%–100.0%. After two doses of cIPV, seropositivity rates reached 100% for all strains. cIPV was well tolerated, with no safety concerns.

Conclusion: Booster vaccination with standalone cIPV induced a robust immune response in Japanese adults.

Trial registration: UMIN, UMIN000013551. Registered 28 March 2014 - Retrospectively registered, https://upload.umin.ac.jp/cgi-bin/ctr/ctr_view_reg.cgi?recptno=R000015830

Background

Polio vaccines can be classified into live attenuated oral polio vaccines (OPVs) and inactivated polio vaccines (IPVs). OPVs are highly effective and safe but also offers several important advantages such as low cost, easy administration, and induction of superior mucosal immunity compared with IPV [1–3]. OPVs have played a leading role in the national immunization program in Japan.

In polio-free areas, concerns have been raised regarding two negative aspects of live attenuated OPVs. One issue is the risk of vaccine-associated paralytic poliomyelitis (VAPP) in persons receiving OPVs and those in contact with them, although this occurs very infrequently [4]. Another issue is the risk of polio outbreaks caused by the regional circulation of vaccine-derived polioviruses (VDPVs), which are highly neurovirulent and transmissible. While OPVs are in use, VAPP and the risk of polio outbreaks caused by VDPVs are unavoidable. Therefore, many polio-free countries have been shifting from OPVs to IPVs [5].

In Japan, routine immunization with OPVs started in 1964 [6]. The national immunization program involved two doses of trivalent OPV (tOPV) consisting of Sabin strains [7, 8]. tOPV was administered at about 4 months and 10 months of age. Few Japanese adults receive polio vaccine boosters following these two doses of tOPV in childhood.

When Japanese adult travelers visit polio-endemic or high-risk areas, we recommend that they receive a booster dose of polio vaccine. In Japan, standalone conventional IPV (cIPV) was approved in 2012, so Japanese adult travelers received standalone cIPV for booster immunizations.

This study aimed to evaluate the immunogenicity of two-dose booster immunization with standalone cIPV derived from virulent strains in Japanese adults.

Methods

1. Study design and subjects

This was a descriptive study performed at Tokyo Medical University Hospital in Japan between May 26, 2011 and August 31, 2016 (UMIN000013551). The study was approved by the ethics committees of the Tokyo Medical University and National Institute of Infectious Diseases, and was conducted following the ethical principles laid out in the Declaration of Helsinki. All subjects provided written informed consent before participating in the study.

Eligible participants were aged 20 years or older. Their childhood polio vaccination history was obtained from immunization records.

Exclusion criteria were pregnancy or breastfeeding, history of poliomyelitis or polio infection, previous IPV vaccination, past history of receiving more than two doses of OPV, known or suspected congenital or acquired immunodeficiency, receipt of immunosuppressive therapy, bleeding disorders, and systemic illness.

During the study, each participant visited Tokyo Medical University Hospital three times. At the first visit, the informed consent form was signed and each participant received cIPV after their eligibility was confirmed. The second and third visits were made between 4 and 6 weeks following the previous visit (Fig. 1).

2. Vaccines

The study vaccine was standalone cIPV (Imovax Polio®, Sanofi Pasteur Inc., Swiftwater, PA, USA. and Imovax Polio® subcutaneous, Sanofi K.K., Tokyo, Japan). In 2011–2012, Imovax Polio® was not approved in Japan, so we imported these vaccines privately. In 2012, Imovax Polio® subcutaneous was approved in Japan, so this vaccine was used in this study. Each subject received ‘Imovax Polio®’

intramuscularly in the deltoid region or 'Imovax Polio® subcutaneous' subcutaneously in the triceps region.

Each vaccine was a trivalent IPV provided in a pre-filled syringe with a needle representing a single dose (0.5 mL). The vaccine contained three types of inactivated poliovirus D-antigens: 40 DU Type 1 (Mahoney strain), 8 DU Type 2 (MEF-l strain), and 32 DU Type 3 (Saukett strain). In addition, 2-phenoxyethanol and formaldehyde were included as preservatives. The vaccines were stored at 2–8 °C.

3. Immunogenicity evaluation and serological analysis

Blood samples (6 mL) were collected in dry sterile capped plastic tubes for assessment of neutralizing antibody titers against polioviruses prior to and 4–6 weeks post-vaccination. Blood was allowed to clot and serum was separated by centrifuging at 3000 rpm for 10 min. The serum samples were stored at ≤ −20 °C.

Immunogenicity was assessed by measuring serum neutralization titers against type 1, 2, and 3 polioviruses in HEp-2 cells using a microneutralization assay. Neutralizing antibody titers were measured at the National Institute of Infectious Diseases (Tokyo, Japan). Viruses included Sabin strains (type 1, 2, and 3), virulent poliovirus strains (type1: Mahoney strain; type 2: MEF-1 strain; and type 3: Saukett strain) and type 2 VDPVs derived from sporadic cases of acute flaccid paralysis in Vietnam in 2012 (SV3128 and SV3130) and from cases from an outbreak in Nigeria in 2005 (11196 and 11198).

The titer of neutralizing antibody required for protection against Sabin strains, virulent poliovirus strains and type 2 VDPVs was assumed to be 1:8 (1/dil) or higher. Neutralizing antibody titers below the threshold of 1:4 were assigned a value of 1:4, and those above the threshold of 1:1024 were assigned a value of 1:1024.

4. Safety

Subjects were observed for 30 min following immunization to assess the occurrence of any immediate adverse events (AEs). Subjects were provided with diary cards to record solicited injection site and systemic reactions as well as other unsolicited AEs. Solicited injection site reactions (pain, erythema, and swelling) and solicited systemic reactions (headache, malaise, myalgia, and fever) were recorded daily for 7 days post-vaccination along with any action taken to manage these AEs. Body temperature was measured daily for 7 days post-immunization. Unsolicited AEs were recorded for 28 days post-immunization.

The intensity of solicited and unsolicited AEs was graded using a three-point scale of increasing severity (grades 1–3). Pain at the injection site was graded as follows: grade 1, no interference with daily activity; grade 2, some interference with daily activity; and grade 3, prevents daily activity. Injection site erythema and swelling were classified as follows: grade 1, ≥ 2.5 and ≤ 5 cm; grade 2, ≥ 5.1 and < 10 cm; and grade

3, ≥ 10 cm. Systemic reactions (headache, malaise, and myalgia) were graded as follows: grade 1, no interference with daily activity; grade 2, some interference with daily activity; and grade 3, prevents daily activity. Fever was defined as axillary temperature ≥ 37.5 °C and was graded as follows: grade 1, ≥ 37.5 °C and ≤ 38.4 °C; grade 2, ≥ 38.5 °C and ≤ 38.9 °C; and grade 3, ≥ 39.0 °C. Serious AEs were recorded throughout the study.

5. Statistical analysis

All statistical analyses were performed using IBM SPSS statistics, version 24 (IBM Corp., Armonk, NY, USA). For immunogenicity assessment, seropositivity rates, geometric mean titers (GMTs) and 95% confidence intervals (CIs) were calculated at Visit 1 (pre-vaccination) and at Visits 2 and 3 post-vaccination with cIPV. Seropositivity was defined as the percentage of subjects with neutralizing antibody titers of ≥ 1:8. For safety evaluation, the numbers and percentage of subjects who experienced at least one AE were calculated.

Results

1. Baseline characteristics of study participants

Sixty-two participants were enrolled in the study. One participant was excluded for the reason of starting treatment of hypercholesterolemia, and the remaining 61 participants were included in the immunogenicity analysis.

The characteristics of the subjects are summarized in Table 1. The 61 subjects comprised 26 men and 35 women with mean ± standard deviation age 35.8 ± 8.0 years.

Table 1
Baseline characteristics of study participants.

Characteristics	Total	Intramascularly	Subcutaneously
Sex	Male: 26 (42.6%)	Male: 20 (40.8%)	Male: 6 (50.0%)
Female	Female: 35 (57.4%)	Female: 29 (59.2%)	Female: 6 (50.0%)
Male			
Age (years)	35.8 (8.0)	35.4 (8.0)	37.3 (7.9)
Mean (SD)	20 : 57	20 : 57	22 : 48
Minimum : Maximum	13 (22.4%)	11 (22.4%)	2 (16.7%)
Age group	33 (59.2%)	29 (59.2%)	4 (33.3%)
20–29	11 (10.2%)	5 (10.2%)	6 (50.0%)
30–39	4 (8.2%)	4 (8.2%)	0
40–49			
50–59			
Year of Birth	19 (31.1%)	18 (36.7%)	1 (8.3%)
1975–1977	42 (68.9%)	31 (63.3%)	11 (91.7%)
Other years			
Doses of Primary OPV	1 (1.6%)	1 (2.0%)	0 (0%)
In childhood	11 (18.0%)	2 (4.1%)	9 (75.0%)
0 dose	31 (50.8%)	28 (57.1%)	3 (25.0%)
1 dose	18 (29.5%)	18 (36.7%)	0 (0%)
2 doses			
Unkown			

2. Immunogenicity

Before booster immunization, the seropositivity rates (defined as neutralization titers > 1:8) were as follows: Sabin 1 (88.5%), Sabin 2 (95.1%), Sabin 3 (52.5%), Mahoney (72.1%), MEF-1 (93.4%), Saukett (31.1%), SV3128 (93.4%), SV3130 (93.4%), 11196 (93.4%), and 11198 (88.5%). The seropositivity rates after the first booster dose were as follows: Sabin 1 (98.4%), Sabin 2 (100%), Sabin 3 (98.4%), Mahoney (98.4%), MEF-1 (100%), Saukett (98.4%), SV3128 (100%), SV3130 (100%), 11196 (100%), and 11198 (100%). The second booster dose resulted in 100% seropositivity rates against all poliovirus strains tested (Fig. 2).

The first booster dose elicited a further increase in neutralizing antibody titers. Only one subject did not achieve a protective level of neutralizing antibodies against poliovirus strains (Sabin 1, Sabin 3, Mahoney, and Saukett) after the first booster dose, but this subject had not received tOPV in childhood.

The GMTs of anti-poliovirus antibodies are shown in Table 2. For the Sabin strains (types 1, 2, and 3), the GMTs increased from 42.0, 44.5 and 10.4 pre-vaccination to 744.9, 914.0 and 560.7 after a single booster dose and to 736.5, 883.4 and 535.8 after two booster doses, respectively. For virulent poliovirus strains (type1: Mahoney strain; type 2: MEF-1 strain; and type 3: Saukett strain), the GMTs increased from 14.9, 40.2 and 6.9 pre-vaccination to 642.6, 924.5 and 494.8 after a single booster dose and to 621.1, 914.0 and 478.3 after two booster doses, respectively. For type 2 VDPVs (SV3128, SV3130, 11196, and 11198), the GMTs increased from 55.2, 37.5, 42.0 and 24.9 pre-vaccination to 956.5, 935.0, 956.5 and 863.5 after a single booster dose and to 956.5, 945.7, 903.7 and 924.5 after two booster doses, respectively(Table 2).

Table 2. GMT of neutralizing antibodies against poliovirus strains.

Total: n=61

Poliovirus		GMT (95%CI)		
		Visit 1	Visit 2	Visit 3
Sabin	Sabin 1	42.0 (29.1; 60.8)	744.9 (589.2; 941.9)	736.5 (603.1; 899.5.2)
	Sabin 2	44.5 (32.7; 60.5)	914.0 (807.6; 1,034.4)	883.4 (774.6; 1,007.4)
	Sabin 3	10.4 (7.6; 14.3)	560.7 (413.8; 759.7)	535.8 (411.7; 697.4)
virulent	Mahoney	14.9 (11.1; 20.1)	642.6 (497.7; 829.7)	621.1 (501.8; 768.8)
	MEF-1	40.2 (30.6; 52.8)	924.5 (828.8; 1,031.2)	914.0 (830.2; 1,006.3)
	Saukett	6.9 (5.4; 8.8)	494.8 (357.2; 685.6)	478.3 (358.3; 638.4)
Type 2 VDPV	SV3128	55.2 (41.3; 73.9)	956.5 (854.1; 1,071.2)	956.5 (871.0; 1,050.5)
	SV3130	37.5 (28.1; 50.1)	935.0 (828.6; 1,055.1)	945.7 (843.0; 1,060.9)
Type 2 VDPV	11196	42.0 (31.5; 56.1)	903.7 (797.4; 1,024.1)	956.5 (854.1; 1071.2)
	11198	24.9 (18.5; 33.6)	924.5 (821.5; 1,040.4)	863.5 (755.7; 986.8)

Intramuscularly: n=49

Poliovirus		GMT (95%CI)		
		Visit 1	Visit 2	Visit 3
Sabin	Sabin 1	47.6 (31.4; 72.0)	739.6 (558.8; 979.0)	729.2 (574.7; 925.3)
	Sabin 2	41.3 (30.1; 56.6)	901.6 (774.6; 1,049.3)	888.9 (762.6; 1,036.2)
	Sabin 3	11.4 (8.1; 16.1)	534.2 (375.3; 760.4)	504.8 (369.1; 690.5)
virulent	Mahoney	16.7 (11.9; 23.5)	624.1 (459.2; 848.3)	633.0 (497.1; 806.1)
	MEF-1	42.5 (31.1; 58.0)	914.4 (800.2; 1,045.0)	901.6 (802.3; 1,013.2)
	Saukett	7.2 (5.6; 9.4)	490.7 (337.4; 713.7)	470.3 (335.6; 659.2)
Type 2 VDPV	SV3128	50.3 (36.2; 69.9)	940.7 (817.1; 1,082.9)	940.7 (837.3; 1,056.8)
	SV3130	34.8 (25.4; 47.8)	914.4 (787.0; 1,062.5)	927.5 (804.0; 1,069.9)
Type 2 VDPV	11196	40.7 (29.5; 56.2)	876.4 (750.8; 1,023.2)	940.7 (817.1; 1082.9)
	11198	26.3 (18.8; 36.6)	901.6 (778.7; 1,043.8)	876.4 (750.8; 1023.2)

Subcutaneously: n=12

Poliovirus		GMT (95%CI)		
		Visit 1	Visit 2	Visit 3
Sabin	Sabin 1	25.4 (11.7; 55.0)	767.1 (538.9; 1092.0)	767.1 (562.1; 1047.0)
	Sabin 2	60.4 (24.8; 147.4)	966.5 (863.1; 1,082.4)	861.1 (674.8; 1,098.8)
	Sabin 3	7.1 (3.3; 15.6)	683.4 (388.0; 1,203.7)	683.4 (462.4; 1,010.1)
virulent	Mahoney	9.5 (5.6; 16.2)	724.1 (507.8; 1,032.4)	574.7 (359.9; 917.7)
	MEF-1	32.0 (18.4; 55.7)	966.5 (863.1; 1,082.4)	966.5 (863.1; 1,082.4)
	Saukett	5.7 (2.9; 11.2)	512.0 (262.3; 999.5)	512.0 (301.7; 868.8)
Type 2 VDPV	SV3128	80.6 (43.8; 148.5)	1024.0	1024.0
	SV3130	50.8 (25.3; 101.9)	1024.0	1024.0
Type 2 VDPV	11196	47.9 (24.8; 92.5)	1024.0	1024.0
	11198	20.2 (10.0; 40.4)	1024.0	812.7 (629.5; 1049.3)

3. Safety

A summary of the safety profile of cIPV is shown in Table 3. No immediate unsolicited systemic AEs were reported. A total of 48 subjects (41.4%) experienced at least one solicited AE. Solicited injection site reactions occurred in 42 subjects (36.2%) and solicited systemic reactions occurred in 13 subjects (11.2%).

Table 3. Adverse events following cIPV boosting.

Symptom	Total	Intramuscularly	Subcutaneously
Immediate adverse events	0 / 122 (0%)	0 / 98 (0%)	0 / 24 (0%)
Solicited reaction	48 / 116 (41.4%)	37 / 92 (40.2%)	11 / 24 (45.8%)
Injection site reaction	42/ 116 (36.2%)	32 / 92 (34.8%)	10 / 24 (41.7%)
Pain	40	30 (grade 1, n=29; grade 2, n=1)	10 (grade 1)
Swelling	15	8 (grade 1)	7 (grade 1, n=6; grade 2, n=1)
Erythema	8	8 (grade 1)	0
Systemic reaction	13 / 116 (11.2%)	8 / 92 (8.7%)	5 / 24 (20.8%)
Fever	0	0	0
Malaise	9	6 (grade 1, n=5; grade 2, n=1)	3 (grade 1)
Headache	5	3 (grade 1)	2 (grade 1)
Myalgia	2	2 (grade 1)	0

The most common solicited injection site reactions were pain (n = 40), swelling (n = 15) and erythema (n = 8). All injection site reactions were either grade 1 or grade 2. The most common solicited systemic reactions were malaise (n = 9), headache (n = 5), and myalgia (n = 2). Fever was not reported. All systemic reactions were either grade 1 or grade 2.

Unsolicited AEs were reported in six subjects, and included upper respiratory tract infection (n = 5), diarrhea (n = 1) and Influenza A (n = 1). These AEs were unrelated to vaccination with cIPV.

Discussion

Since the World Health Organization (WHO) launched the global polio eradication program in 1988, the number of polio cases caused by wild polioviruses has steadily decreased worldwide from a 1988

estimate of approximately 350,000 cases to 175 cases in 2019 [9].

On May 5, 2014, the WHO stated that the international spread of wild polioviruses is a Public Health Emergency of International Concern (PHEIC) [10]. As of 2020, WHO has agreed that the risk of international spread of poliovirus remains a PHEIC. Preventing the spread of wild polioviruses as well as polio outbreaks caused by cVDPV are both important elements of polio eradication strategies [11, 12].

The Polio Eradication and Endgame Strategic Plan 2013–2018 represented a major milestone toward polio eradication and describes the specific steps required to successfully achieve eradication [13]. This plan called on countries to strengthen routine immunization programs, to introduce at least one dose of IPV into routine immunization schedules, and to withdraw OPV in a phased manner starting with the replacement from type 2 strain-containing trivalent OPV to bivalent OPV [14, 15].

As of September 2012 in Japan, all infants are immunized with IPV (either stand-alone or in combination with diphtheria, tetanus, and pertussis vaccines) rather than tOPV from the Sabin strain. In the current schedule, four doses of IPV are administered.

Worldwide, the prevailing wisdom is that most adults do not need polio booster vaccination if they were previously vaccinated as part of routine immunization schedules [16, 17]. However, adults at higher risk should consider polio vaccination if they fall into the following groups: (i) travelers to polio-endemic or high-risk areas, (ii) workers in facilities that handle poliovirus infectious materials, and (iii) healthcare workers treating patients who could have polio or be in close contact poliovirus-infected individuals. Adults meeting these criteria who previously received one or two doses of poliovirus vaccine should receive an additional one or two doses. The time elapsed since the earlier dose(s) is immaterial.

Generally, routine poliovirus immunization schedules involve three or more doses worldwide, but most Japanese adults received only two doses of tOPV in childhood according to the national immunization program in Japan. As such, they have not completed the typical polio vaccine series as defined abroad [18].

In our study, we found that polio neutralization titers before cIPV vaccination in most Japanese adults were maintained at protective levels. This result shows that tOPV is effective in conferring durable protection against paralytic poliomyelitis. Because passively acquired booster effects resulting from natural contact with circulating polioviruses is limited in Japan, this suggests that most Japanese adults vaccinated against polio during infancy will maintain life-long immunity against the virus. However, neutralizing antibody titers against the Sabin 3 and Saukett strains were relatively low. In addition, titers against the Sabin 1 strain were relatively low in individuals born between 1975 and 1977 (additional file 1). This trend was consistent with previous data reported by the National Institute of Infectious Diseases [19, 20].

In Japan, booster polio vaccination is not recommended for adults who have received two doses of tOPV. However, Japanese adult travelers entering polio-endemic or high-risk areas should receive one or two

booster immunizations with cIPV.

Following booster vaccination, antibody titers increased significantly and reached a protective level against all strains. In individuals who had only received a single dose of OPV, booster immunization with cIPV was effective in enhancing antibody titers. Antibody titers after two booster doses were elevated in all subjects whose immunization histories were unknown.

Neutralizing antibodies were efficiently induced regardless of the route of injection, and seroconversion did not depend on age or sex. Another study suggested that individual-level immunity may be better maintained when an OPV primary immunization is boosted by IPV [21].

During the study, no immediate systemic AEs were reported. Overall, 36.2% of subjects experienced at least one solicited injection site AE (e.g., erythema, swelling, and pain). Moreover, 11.2% of subjects experienced at least one solicited systemic AE (e.g., malaise, fever, headache, and myalgia). Unsolicited AEs were reported in six subjects, and included upper respiratory tract infection (5 subjects), diarrhea (1 subject) and Influenza A (1 subject). These AEs were unrelated to vaccination with cIPV.

Several limitations of our study need to be considered before making any generalizations. First, this was a single site study with a small sample size and the genders were not balanced. Nevertheless, poliovirus antibodies were significantly increased in all subjects following cIPV booster vaccination.

In summary, this study assessed the immunogenicity of a two-dose booster regimen of cIPV in Japanese adults. Seropositivity against wild, virulent and type 2 VDPV strains of poliovirus was achieved in 100% of study participants who two booster doses of cIPV. The GMT of antibodies induced following administration of the two-dose booster cIPV regimen was high. The cIPV booster was safe and immunogenic in previously tOPV-immunized adults.

List Of Abbreviations

conventional inactivated polio vaccine (cIPV)

live attenuated oral polio vaccines (OPVs)

inactivated polio vaccines (IPVs)

vaccine-associated paralytic poliomyelitis (VAPP)

vaccine-derived polioviruses (VDPVs)

trivalent OPV (tOPV)

geometric mean titers (GMTs)

confidence intervals (CIs)

Public Health Emergency of International Concern (PHEIC)

Declarations

Ethics approval and consent to participate

This study was conducted following review and approval by the Ethics Committee of Tokyo Medical University and National Institute of Infectious Diseases. Respondents provided written informed consent and voluntarily participated in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing Interests

S. Fukushima, A. Hamada and H. Simizu declare no conflicts of interest associated with this study and manuscript. T. Nakano received honoraria from Daiichi Sankyo Co. and Sanofi K.K.

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Authors' contributions

All authors participated in the drafting, review, and approval of the manuscript.

S. Fukushima: study concept and design, interpretation of data, and preparation of the manuscript. T. Nakano, A. Hamada: study concept and design, interpretation of data, and preparation of the manuscript. H. Shimizu: analysis and interpretation of data, and preparation of the manuscript.

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Figures

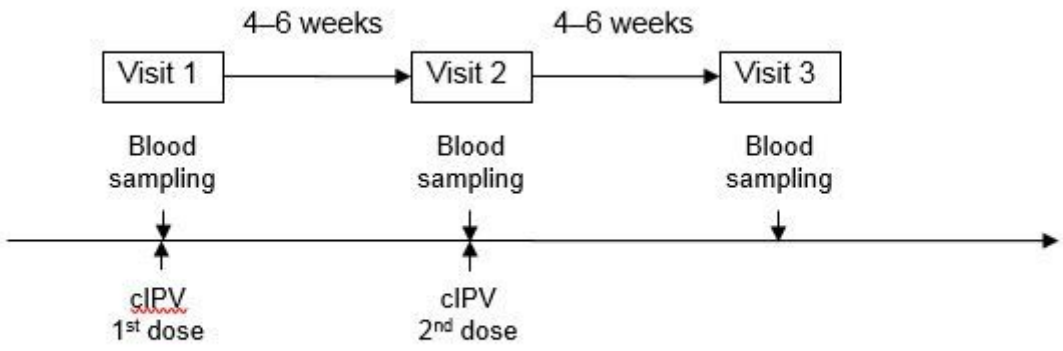
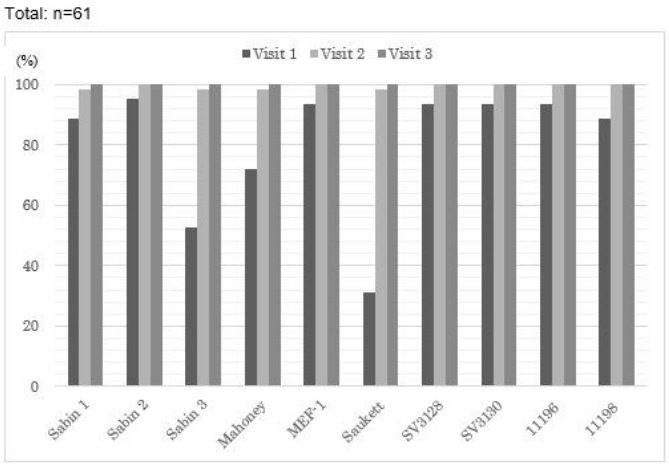
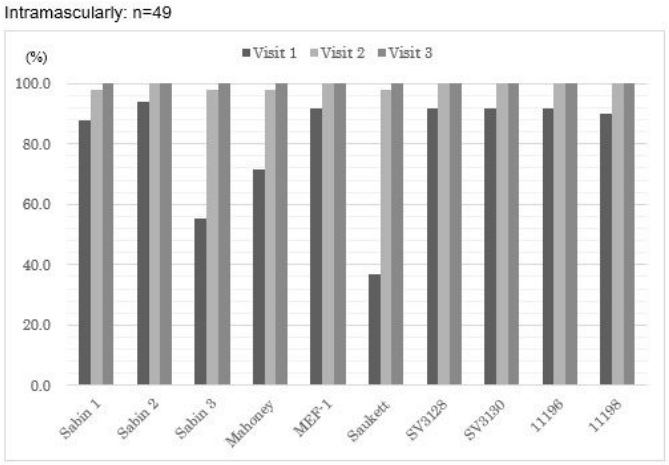


Figure 1

Study protocol. Note: At Visit 1, each subject received cIPV intramuscularly in the deltoid region or subcutaneously in the triceps region. Visits 2 and 3 were made 4–6 weeks following Visits 1 and 2, respectively. Blood samples were collected for assessment of antibody titers against poliovirus at Visits 1, 2 and 3.





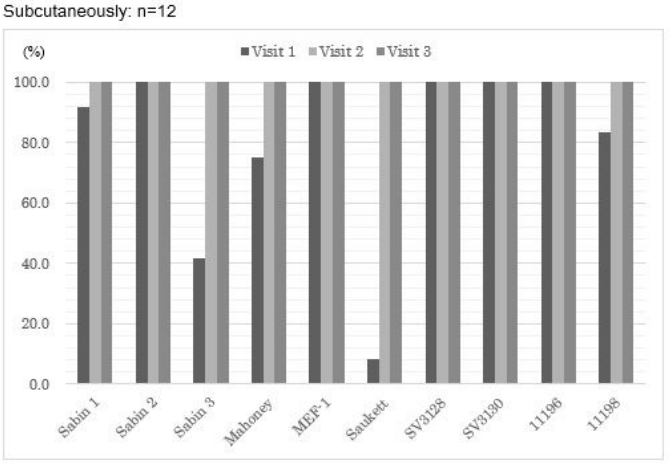


Figure 2

seropositivity rate pre-cIPV boosting (Visit 1) and following one (Visit 2) and two (Visit 3) booster doses.

Supplementary Files

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