

Immunogenicity and safety profile of a primary dose of bivalent oral polio vaccine given simultaneously with DTwP-Hb-Hib and inactivated poliovirus vaccine at the 4th visit in Indonesian infants

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ABSTRACT

In this study, we aimed to evaluate the immunological protectivity of infants following four doses of bivalent oral polio vaccine (bOPV; Bio Farma), which were given simultaneously with DTwP-Hb-Hib (Pentabio[®]), along with one dose of inactivated poliovirus vaccine (IPV) at the fourth visit. A total of 143 newborn infants who fulfilled the inclusion criteria were enrolled and completed the study. Subjects received the first dose of bOPV at birth. On days 60, 90 and 120, bOPV was given simultaneously with Pentabio[®]. On day 120, one dose of IPV was also administered. Serum samples for serology analysis were collected before the first dose of bOPV (at day 0), before the second dose of bOPV (at day 60) and 30 days after the last dose of bOPV. In addition, the intensity, duration and relationship of each adverse event to the trial vaccines were assessed. Seroprotection rates after the fourth dose of bOPV were 100%, 91.6% and 99.3% for poliovirus P1, P2 and P3, respectively. Seroconversion rates after the fourth dose of bOPV were 100.0%, 93.3% and 100% for poliovirus P1, P2 and P3, respectively. There were no severe adverse events, and systemic reactions were generally mild during the 1–28 day post-vaccination period. Collectively, our findings indicate that bOPV given simultaneously with Pentabio[®] and one dose of IPV at the 4th visit was immunogenic and well tolerated.

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1. Introduction

Issues have been documented with the oral polio vaccine (OPV), namely, the occurrence of vaccine-associated paralytic poliomyelitis (VAPP) and circulating vaccine-derived poliovirus (cVDPV). The incidence of VAPP is approximately 1 in 2.7 million doses of the OPV. In addition to VAPP, the live poliovirus strains present in the OPV, currently predominantly Sabin type 2, on rare occasions can revert to a form that may be able to cause paralysis in humans and develop the capacity for sustained circulation (cVDPV), which

Abbreviations: GMT, geometric mean titre; GPEI, global polio eradication initiative; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine; VAPP, vaccine-associated paralytic poliomyelitis; cVDPV, circulating vaccine-derived poliovirus; WHO, World Health Organization.

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is associated with sustained person-to-person transmission. These are considered threats to polio eradication that are not issues with the use of the inactivated poliovirus vaccine (IPV) [1]. Thus, as long as the OPV is used, there is a risk of cVDPV causing poliomyelitis outbreaks in unprotected communities, which would threaten the global goal of poliovirus eradication [2,3].

With ongoing polio outbreaks in several African and Asian countries, polio eradication remains a challenge. Since declared to be free from polio in 2014, Indonesia has confirmed 1 case of cVPDV1 in 2019 with onset of paralysis in 2018. African countries such as Angola, Central African Republic, Ethiopia, Ghana, Nigeria, Democratic Republic of the Congo, Togo and Somalia currently are facing cVDPV outbreaks. Afghanistan and Pakistan are affected by both wild polio virus and cVPDPV outbreaks. In 2019, cVDPV cases also reported from several Asian countries such as Myanmar, China and Philippines [4].

In May 2013, the World Health Assembly endorsed *The Polio Eradication & Endgame Strategic Plan 2013–2018*, developed by the Global Polio Eradication Initiative (GPEI) to complete the

eradication and containment of all wild, vaccine-derived and Sabin polioviruses worldwide. Three essential features of the GPEI strategic plan are (a) the withdrawal of the type-2 OPV strain from tOPV and the introduction of bOPV (types 1 and 3), (b) the introduction of the routine use of the IPV to manage long-term poliovirus risks, including type-2 cVDPV and (c) the cessation of all OPV use following/in accordance with the global certification of total WPV serotype eradication. To manage the risks associated with the removal of the type-2 component of OPV, such as the emergence of cVDPV or the re-introduction of the wild-type 2 poliovirus, the WHO Strategic Advisory Group of Experts recommended that all OPV-using countries introduce at least one dose of IPV into their routine immunisation programmes [5].

Following the recommendations of the Expanded Program on Immunisation, the Indonesian National Immunisation schedule comprises the primary vaccination of bOPV at birth, with three doses of DTwP-HB-Hib at 2, 3 and 4 months and the IPV at 4 months of age [6,7]. To comply with the national immunisation programme, we performed this bOPV study simultaneously with Pentabio®. Therefore, The objective of this study was to evaluate the immunogenicity and safety profile of the primary dose of bOPV (Bio Farma), which was given simultaneously with the DTwP-HB-Hib vaccine (Pentabio®), along with the IPV at the 4th visit, in Indonesian infants.

Bio Farma supplies the bOPV to support *The Polio Eradication & Endgame Strategic Plan* in Indonesia and globally. The Pentabio® vaccine, which is used simultaneously with bOPV, has been proven in a previous study to be immunogenic and well tolerated by healthy infants aged 6–11 weeks at the first dose of the vaccine [8].

2. Materials and methods

2.1. Study design and population

This study was an open blind, prospective intervention, phase IV study that was conducted from May 2016 to May 2017 in Bandung, Indonesia. The recruited subjects were healthy, full-term, newborn infants. Exclusion criteria included mild, moderate, or severe illness, especially infectious diseases or fever (axillary temperature ≥ 37.5 °C on day 0) and a history of acquired immunodeficiency (including HIV infection). In addition, infants who were immunised with nonscheduled bOPV or IPV during the trial, as well as those requiring hospitalisation at birth, were excluded.

All subjects were recruited based on written informed consent provided by the parents or their legally acceptable representative (s) after the explanation of the trial, including the nature of the trial, potential risks and his/her obligations. The study protocol was approved by the Research Ethics Committee of the Medical Faculty Universitas Padjadjaran, the Quality Assurance Division of Bio Farma and Indonesian Regulatory Authorities. This trial was conducted in accordance with ICH Good Clinical Practice guidelines,

the Declaration of Helsinki and local regulatory requirements [9,10].

2.2. Study procedure

The immunisation schedule in this study followed the Indonesian National Immunisation schedule (Table 1). A total of 150 newborn infants who fulfilled the inclusion criteria were enrolled in this trial and received the first dose of bOPV at birth. The infants received bOPV simultaneously with Pentabio® on days 60 and 90. On day 120, the infants received bOPV plus IPV and the third dose of Pentabio®. Serum samples were collected for antibody determination by neutralisation testing with the standard poliovirus using Hep-2 cell lines. Samples were collected at visit 0 before vaccination (pre-dose), at visit 2 which is 60 days after the first dose of the study vaccine (post 1st dose) and at visit 5 which is 30 days after the last dose of the study vaccine (post 4th dose). All sera samples were blinded and randomised before testing.

The subjects' parents or representatives kept an observation card (i.e. a diary) to assess and record information on local and systemic reactions for 30 days following immunisation, with special attention paid on the first 3 days after vaccination. Serious adverse events that occurred throughout the trial period were reported immediately to the sponsor and the Ethics Committee and recorded in the Case Report Form [11].

2.3. Study vaccine

The bOPV batch number 2042015 used in this study was manufactured by Bio Farma, Bandung, Indonesia. In this formulation, each dose of bOPV administered orally corresponded to 2 drops (0.1 mL) containing live attenuated poliovirus of the Sabin strain (type 1 $> 10^{6.0}$ CCID₅₀; type 3 $> 10^{5.8}$ CCID₅₀), 35% v/v sucrose, erythromycin ≤ 20 µg/mL, kanamycin ≤ 100 µg/mL and acetic acid at pH 6.5 ± 0.1 [12].

The Pentabio® used in this study was also manufactured by Bio Farma. Pentabio® was administered intramuscularly in the anterolateral aspect of the right thigh. Each 0.5-mL dose of the Pentabio® vaccine contained ≥ 30 IU of purified diphtheria toxoid, ≥ 60 IU of purified tetanus toxoid, ≥ 4 IU of inactivated *Bordetella pertussis*, 10 µg hepatitis B surface antigen (recombinant), 10 µg Hib in the form of polyribosil-ribitol-phosphate conjugated to the tetanus toxoid, 0.33 mg aluminium phosphate, 4.5 mg sodium chloride and 0.025 mg thimerosal. In this formulation, aluminium phosphate works as an adjuvant, whereas thimerosal acts as a preserving agent [13].

The IPV vaccine (ShanIPV™) used in this study was manufactured by Shantha, Hyderabad, India. The IPV was administered intramuscularly in the anterolateral aspect of the left thigh. Each 0.5-mL dose of the ShanIPV® vaccine contained type 1 (Mahoney strain) 40 DU, type 2 (MEF-1 strain) 8 DU and type 3 (Saukett strain) 32 DU, with the excipients 2-phenoxyethanol, formaldehyde, ethanol and medium 199 Hanks (containing particular amino acids, mineral salts, vitamins, glucose, polysorbate 80 and water for injection) and hydrochloric acid or sodium hydroxide for pH adjustment [14].

Vaccines were stored in the refrigerator at a temperature of +2° to +8 °C (as recommended) at the clinical trial centre to ensure quality.

2.4. Blood sampling and antibody measurement

For each sampling, 4 mL of blood was collected in vacutainer tubes at visit 0 (pre-dose), visit 2 (post 1st dose) and visit 5 (post 4th dose). After clotting at room temperature for 30 min to 2 h, blood samples were centrifuged at 3000 rpm for 15 min, and the

Table 1
Vaccination schedule.

0–3 days of age	2 months of age	3 months of age	4 months of age
Hepatitis B (birth dose)	bOPV	bOPV	bOPV
bOPV	DTP-HB-Hib (Pentabio®)	DTP-HB-Hib (Pentabio®)	DTP-HB-Hib (Pentabio®) IPV

bOPV: bivalent (P1 and P3) oral polio vaccine.

DTP-HB-Hib: Diphtheria-Pertussis-Tetanus-Hepatitis B-Haemophilus Influenza type B.

IPV: inactivated polio vaccine.

sera were stored in cryotubes within 24 h after the sampling. The sera samples were rapidly stored in a freezer at $-20\text{ }^{\circ}\text{C}/-80\text{ }^{\circ}\text{C}$ until testing. Each blood sample was labelled to indicate the blood sampling stage, inclusion number and infant initials.

Antibody titre measurements were determined by neutralisation assays. Serum with poliovirus-neutralising antibodies measurable at a dilution of 1:8 or above was defined as seropositive. The transition from seronegative to seropositive was also evaluated. For infants who were seronegative at enrolment, a change to seropositive (>8) was considered a seroconversion. For subjects who were protective at enrolment, seroconversion was defined as a four-time increase of antibody over the pre-dose samples. Assays were performed at the Clinical Trial Laboratory of Bio Farma. The Quality Assurance of Bio Farma has been validated and approved for these procedures [15,16].

2.5. Safety assessment

The subjects' parents were provided with a thermometer and observation card to assess and record on the occurrence of any systemic adverse events (solicited and unsolicited) within 30 days following vaccination. Solicited systemic adverse events are fever, irritability, vomiting, diarrhoea and acute flaccid paralysis. Safety data from the diary card were controlled by a visit of the subjects to the clinic or by a visit of the nurse (or field visitor) to the subjects' homes or by a call to the parents.

Local reactions were assessed at the vaccination site. Fever was assessed through daily axillary temperature readings (the parents or representatives of the subjects were supplied with a thermometer and were instructed as to how to use it) and any other systemic complaints. Any medical office visit, emergency room visit, or hospitalisation for any reason was recorded throughout the trial period.

2.6. Sample size determination and statistical analysis

Sample size was determined based on 95% confidence interval. The required sample size was 150 including 5% of drop out anticipation.

The immunogenicity analyses were performed on the per-protocol population. The safety analyses were based on the intention-to-treat population analyses. All included and vaccinated subjects were analysed.

3. Results

3.1. Study population

Of the 150 subjects enrolled at visit 1, 143 subjects completed the study and were analysed per the protocol for immunogenicity analyses (Fig. 1).

One hundred and fifty subjects were included in the full analysis set for safety analyses. Demographic and baseline characteristics of the subjects are presented in Table 2.

3.2. Immunogenicity assessment

3.2.1. Seroprotection to polio virus types 1, 2 and 3

At pre-dose, post 1st dose and post 4th dose, the seroprotection rates for P1 were 62.2%, 81.1% and 100%, respectively; for P2, these values were 89.5%, 48.3% and 91.6%, respectively; and for P3, these values were 51.7%, 55.9% and 99.3%, respectively (Table S1).

3.2.2. Seroconversion to anti-poliovirus types 1, 2 and 3

At post 1st dose, 77.8%, 0.0% and 47.8% subjects were considered to have seroconverted to poliovirus types 1, 2 and 3, respectively. At post 4th dose, 100%, 93.3% and 100% subjects were seroconverted to polio types 1, 2 and 3, respectively (Table S2).

3.2.3. Geometric mean titre (GMT) of anti-poliovirus types 1, 2 and 3

The administered vaccines induced an increase in the GMTs at post 4th dose for the anti-poliovirus type P1 and P3 versus baseline; for anti-P1: from 9.66 (7.20–12.96) to 1495.55 (1294.79–1727.85) and for anti-P3: from 4.85 (3.77–6.24) to 846.45 (727.11–985.14).

The GMT for anti-P2 at post 4th dose was 23.45 (20.02–27.45), slightly decreased from its pre-dose value at 28.83 (23.10–35.99). At post 4th dose, The GMT for anti-P2 was the lowest compared to anti-P1 and anti-P3 (Fig. 2). However, this result has been increased from anti-P2 GMT at post 1st dose of study vaccine (4.73 (3.69–6.06)) (Table S3).

3.2.4. Percentage of subjects with increasing antibody titres ≥ 4 times for anti-poliovirus types 1, 2 and 3

We observed increased antibody titres (≥ 4 times) post 1st dose compared with the pre-dose, corresponding to 60.1%, 0.0% and 39.9% for P1, P2 and P3, respectively. In addition, there were increasing antibody titres (≥ 4 times) post 4th dose compared with the pre-dose, corresponding to 97.2%, 16.1% and 97.9% for P1, P2 and P3, respectively (Table S4).

3.3. Safety assessment

3.3.1. Systemic adverse events 30 min after the 1st, 2nd, 3rd and 4th doses of vaccination

The most frequent systemic adverse event within 30 min after immunisation was irritability, which occurred in 0.0%, 2.7%, 2.1% and 0.7% subjects after the 1st, 2nd, 3rd and 4th doses of vaccination, respectively.

3.3.2. Systemic adverse events > 30 min to 72 h after the 1st, 2nd, 3rd and 4th doses of vaccination

The most common systemic adverse events within 30 min to 72 h after immunisation were irritability and fever. Irritability occurred in 9.7%, 23.6%, 16.7% and 19.6% subjects after the 1st, 2nd, 3rd and 4th doses of vaccination, respectively. Fever occurred in 6.2%, 16.7%, 7.6% and 15.4% subjects after the 1st, 2nd, 3rd and 4th doses of vaccination, respectively.

3.3.3. Systemic adverse events > 72 h to 30 days after the 1st, 2nd, 3rd and 4th doses of vaccination

Irritability occurred in 0.0%, 0.7%, 0.7% and 2.8% subjects after the 1st, 2nd, 3rd and 4th doses of vaccination, respectively.

Fever occurred in 0.0%, 1.4%, 1.4% and 4.2% subjects after the 1st, 2nd, 3rd and 4th doses of vaccination, respectively.

Based on the above systemic assessment results, the incidence of systemic reactions was the lowest after the 1st vaccination of bOPV. The percentage of systemic reactions increased after the bOPV was given simultaneously with Pentabio[®] at the 2nd and 3rd doses and the IPV at the 4th dose (Fig. 3).

3.3.4. Systemic reaction intensity

The majority of adverse events were considered mild and resolved spontaneously within the 72-hour follow-up period. There was no acute flaccid paralysis case reported. During the study, seven subjects were hospitalised. All serious adverse events were reported to the Research Ethics Committee of the Medical Faculty Universitas Padjadjaran Bandung and the Regional Committee of Adverse Events Following Immunisation West Java

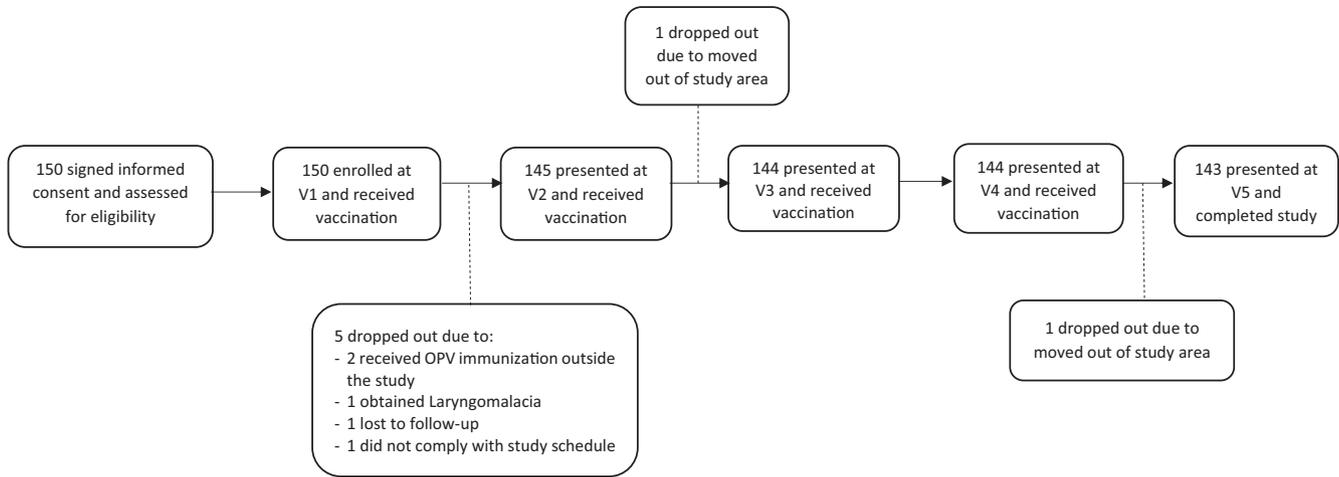


Fig. 1. Subjects assessable at each step of the study.

Province, who audited the cases and determined they were a coincidence and not related to the vaccine.

4. Discussion

The Polio Endgame Strategy in Indonesia aims to support and strengthen the routine vaccination programme through the Polio National Immunisation Week in March 2016, which targeted children aged 0–59 months. In this initiative, on 4 April 2016, steps were taken to switch from tOPV to bOPV, which contains just types 1 and 3 and was continued by introducing the IPV into the routine immunisation programme in July 2016 all over Indonesia, except in the Yogyakarta province where the IPV was introduced in September 2007. The main goal of the Polio Endgame Strategy is to eventually completely withdraw the OPV and replace it with the IPV in the routine immunisation schedule [5,7,17].

Table 2 Summary of subject demographic characteristics (full analysis set).

Description	Total
N included	150
Gender	
Male, n (%)	82 (54.7)
Female, n (%)	68 (45.3)
Age (days)	
Mean (SD)	0.57 (0.64)
Min; max	0; 3

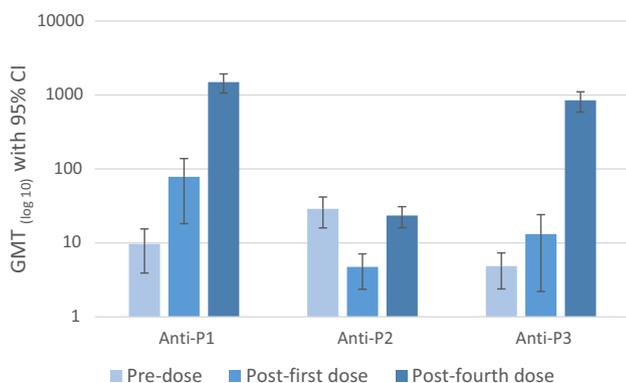


Fig. 2. Geometric mean titers (GMT) of anti-poliovirus types 1, 2, and 3 at pre- and post-vaccination.

4.1. Immunogenicity

Our study confirmed that after receiving the primary dose per the immunisation schedule (endgame polio), seroprotection rates were high at 100.0% for P1 (95% CI: 97.4–100.0%), 91.6% for P2 (95% CI: 85.9–95.1%) and 99.3% for P3 (95% CI: 96.1–99.9%).

The seroconversion rates found in this study are similar to those of another study that found the new routine polio endgame immunisation schedules using bOPV and one IPV dose provide higher levels of seroconversion for types 1 and 3 poliovirus, but lower levels of seroconversion for type 2 poliovirus [18]. The seroconversion results in this study are also similar to previous studies of tOPV [17,19]. Seroconversion to P1 in this study was exactly the same as that in the mOPV1 study at 100% [20].

The GMTs also increased for anti-P1 and anti-P3 (Table S5). GMT for anti-P2 was decreased at post 1st dose of bOPV compared to baseline at birth. This is expected since bOPV did not contain antigen to poliovirus type 2. After last dose of study vaccination, there was an increment of GMT for anti-P2 from 4.72 to 23.45; even though it was not as high as anti-P1 and anti-P3 since the subjects only received one dose of vaccine with P2 strain compared to five doses of vaccine with P1 and P3 strains.

This result is similar with study by Saleem et al (2017) in Pakistan, where antibody titer at 8 weeks post vaccination with IPV were found much higher for anti-P1 and anti-P3 compared to anti-P2 [21].

In this schedule, all subjects received only one dose of P2 in IPV, but seroprotection was determined to be high (91.6%) with 93.3% subjects have seroconversion to type 2 poliovirus. However, only 16.1% of the subjects had increasing antibody titres (≥ 4 times) for type 2 poliovirus. Based on a systematic review and meta-analysis study on 12 published articles by Nicholas Grassly, after a single dose of IPV, 33%, 41% and 47% of children seroconverting to P1, P2 and P3, respectively. After given 2 doses of IPV, 79%, 80% and 90% of children seroconverting to P1, P2 and P3, respectively [22].

One study documented that following the administration of a second IPV dose six months after first dose at birth, a considerable proportion of babies responded with neutralizing antibody to the three poliovirus type. The anamnestic response should provide the basis for protection against paralytic poliomyelitis in case of exposure to wild poliovirus later in life [23].

Considering the relatively low GMT value and the low percentage of four-fold increases after the post 4th dose for P2, a further assessment is considered necessary to analyse the protection duration toward P2 following the immunisation schedule used in this

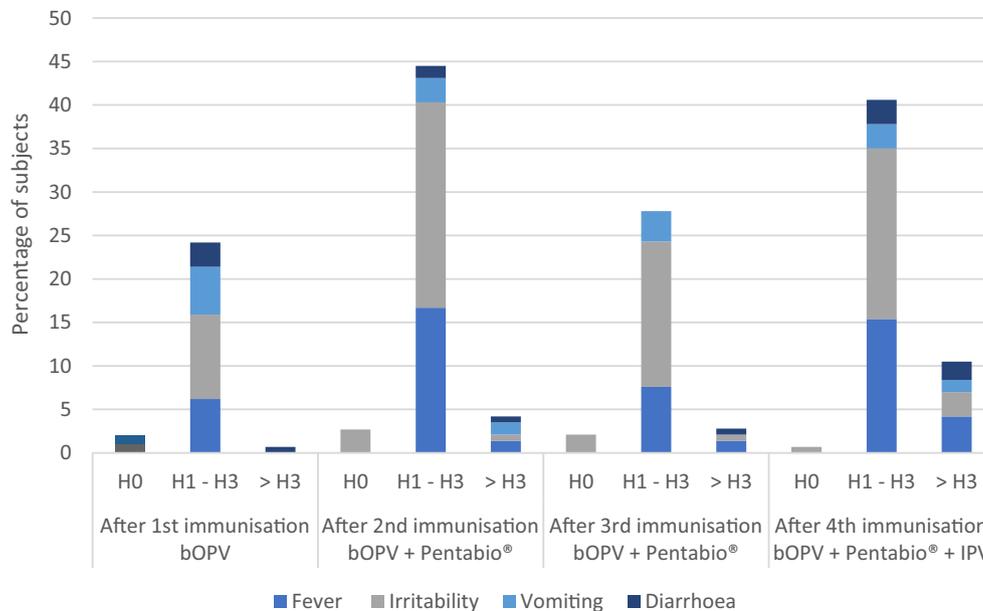


Fig. 3. Percentage of subjects reported solicited systemic adverse events after each vaccination. Occurrence of systemic adverse events after each vaccination were categorized into three time points: H0 (30 min post-vaccination), H1-H3 (>30 min – 72 h post vaccination) and >H3 (>72 h – 30 days post vaccination).

study. Further studies are also considered important to assess whether adding the IPV dose into the current routine immunisation schedule increases the protectivity against P2.

4.2. Safety

The safety of bOPV was determined during the birth dose, and no systemic events were reported within 30 min after immunisation. Between days 1 and 3, 6.2% and 9.7% of the subjects experienced fever and irritability, respectively. After the second and the third doses of bOPV given simultaneously with Pentabio®, fever was found in 11%–24% subjects and irritability was reported in 24%–34% subjects, both at higher rates than at the birth dose of bOPV. The results of this study were not too different from the Pentabio® Phase III study, where fever was found in 18.9–29.3% subjects and irritability was reported in 28.2–53.0% of the subjects [8]. Adverse events are reflected as simultaneous immunisations of bOPV and Pentabio® for the second and third doses of bOPV and with the additional IPV given with the fourth dose of bOPV.

This study has a limitation due to the fact that the bOPV and IPV were administered simultaneously with Pentabio® and the hepatitis B vaccine within the national vaccine programme schedule. Therefore, the bOPV safety profile obtained from the study may not present the actual bOPV and IPV safety profile. Another limitation is that there was no control group in this study.

5. Conclusions

The trial vaccine bOPV given simultaneously with Pentabio®, along with one dose of IPV at the 4th visit was considered immunogenic and well tolerated, with no vaccine-related serious adverse events reported during the trial.

Author Contributions

KR was the principal investigator. KR, EF, MD, RT, NSB and RMS conceived the study and its design. KR, EF, MD and RT conducted the study and recruited the subjects. EF and MD wrote and reviewed the manuscript. CBK was the medical adviser and

reviewed the study and the manuscript. All authors have read and approved the final manuscript.

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CRediT authorship contribution statement

Eddy Fadlyana: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Meita Dhamayanti:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **Rodman Tarigan:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing – review & editing. **Rini M. Sari:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Validation. **Novilia S. Bachtiar:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Cissy B. Kartasasmita:** Conceptualization, Methodology, Writing – review & editing. **Kusnandi Rusmil:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Interest

Novilia Sjafrri Bachtiar and Rini Mulia Sari are employees of PT. Bio Farma. Novilia Sjafrri Bachtiar is the Head of the surveillance and clinical trial division of PT. Bio Farma, Rini Mulia Sari is the Head of the clinical trial sub-division of PT. Bio Farma.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2020.01.007>.

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