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One-month follow up of a randomized clinical trial-phase II study in 6 to <24 months old Indonesian subjects: Safety and immunogenicity of Vi-DT Typhoid Conjugate Vaccine

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ABSTRACT

Introduction: World Health Organization estimates the annual global incidence of typhoid fever at 11-21 million cases and approximately 128 000 to 161 000 deaths. The currently used Vi-polysaccharides (Vi-PS) vaccines have been proven to be safe and efficacious in children 2 years and above. However, poor immunogenicity of Vi-PS was observed in children below 2 years of age. This Phase II study is the continuation of the previously published Phase I study that aims to evaluate the safety and immunogenicity of a novel Vi-DT Typhoid Conjugate Vaccine (Bio Farma) in subjects 6 to <24 months.
Methods: An interventional, blinded, comparative, randomized phase II study was conducted from July 2018 until January 2019. There were 200 healthy subjects divided into two groups: trial and control groups. Inactivated poliovirus vaccine was given to control group. Immediate and delayed local and systemic reactions up to 28 days post vaccination were recorded. Antibody titers were measured prior to vaccination (V1) and 28 days post vaccination (V2).
Result: The study showed that the seroconversion of Vi-DT vaccine 98.99%. One dose of Vi-DT vaccine induced higher geometric mean titers (GMT) in all subjects compared to that of baseline. Pain was the most common immediate and delayed local reaction. Immediate and delayed systemic reactions that mostly occurred was fever. There were no serious adverse events reported within 28 days post vaccination.
Conclusion: The novel typhoid Vi-DT conjugate vaccine is safe and immunogenic in children 6 to <24 months.
Trial registration number: NCT03460405.

Introduction

Typhoid fever, which is caused by enteric bacterium, *Salmonella enterica* serovar Typhi, is an acute generalized infection. WHO estimates the annual global incidence of typhoid fever at 11-21 million cases and approximately 128 000 to 161 000 deaths (World Health Organization, 2018). Children are the most affected age group with a peak incidence known to occur in individuals aged 5 to <15 years of age (World Health Organization, 2018; Pitzer et al., 2014).

However, children below 2 years are also affected. Based on Strategic Advisory Group of Experts (SAGE) on immunization data from 15 sources in Africa, Asia and America showed that among 0–60 months age groups, 27% of typhoid fever occurred in 0-4 years age group, including 29.7% of typhoid fever episodes in the below 2-year age group, 9.9% in the below 1-year age group and 2.9% in infants below 6 months (Background paper to SAGE on Typhoid Vaccine Policy Recommendation, 2017). These data are

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supported by a cohort study in Pakistan where from the total of all culture-positive *Salmonella* Typhi (*S.* Typhi) cases, 43.7% occurred in children below2 years old. The incidence of typhoid bacteremia in children below 2 years of age was 443.1 (95% CI: 193.8–876.5) per 100,000 child-years and in infants under 12 months of age was 506.4 cases per 100,000 child years (95% CI: 160.9–1222.0) (Owais et al., 2010).

A study was conducted in Hasan Sadikin Hospital, West Java, Indonesia to evaluate the incidence of typhoid fever in hospitalized under-five children. Out of 108 culture positive patients with typhoid fever, a majority of patients (90.74%) fell under the 2-5-year-old age group whereas 9.26% were under 2 years (Setiabudi and Madiapermana, 2005). Another study was conducted in Dr Sardjito General Hospital, Yogyakarta, Indonesia to evaluate the incidence of culture positive and serology positive typhoid fever in hospitalized patients. This study showed that 7% of typhoid patients were below 2 years old (Lestari and Arguni, 2017). Although incidence of typhoid fever in children below 5 years is not as high as school-aged children, a systemic review of enteric fever showed that mortality rate from enteric fever is higher amongst children below 5 years of age compared to those above 5 years (Britto et al., 2017; Azmatullah et al., 2015)

Symptoms of typhoid infection include fever which lasts one to four weeks. Fever is accompanied by chills, headache, malaise, anorexia, nausea, abdominal pain, dry cough and myalgia (Paul and Bandyopadhyay, 2017; Capeding et al., 2018). About 1-2% of hospitalized cases result in death (Pitzer et al., 2014; Capeding et al., 2018). Due to the high incidence of typhoid in developing countries predominantly in Asia and Africa, and moreover the increasing rates of antimicrobial resistance (AMR), prevention has become a global health priority (Jamka et al., 2019; Sahastrabuddhe and Saluja, 2019).

Antimicrobial resistance is becoming common among *S. Typhi* strains spreading from South Asia to Africa. These *S. Typhi* strains are resistant to first line antibiotics such as cotrimoxazole, ampicillin and chloramphenicol as well as fluoroquinolones. Some β lactamase-producing strains have also been identified, contributing to treatment failure. Therefore, prevention using vaccinations is crucial in the management of typhoid (Jin et al., 2017; Andrews et al., 2018; Meiring et al., 2018).

Vaccines that are available today are either non-immunogenic in early childhood, such as parenteral Vi capsular polysaccharide vaccine, or are unsuitable for children younger than 5 years, such as Ty21a which is an oral live attenuated typhoid vaccine. Ty21a is unsuitable for use in children below 5 years of age because it comes in capsules which are difficult for young children to swallow (Britto et al., 2017; Jin et al., 2017; Mohan et al., 2015).

Due to the high incidence of typhoid fever in children below 2 years, SAGE recommends the use of Typhoid Conjugate Vaccines (TCV) in children below 2 years (Background paper to SAGE on Typhoid Vaccine Policy Recommendation, 2017). TCVs, which combine the Vi-polysaccharide capsule with a protein carrier, are immunogenic and can be used in early infancy (Jin et al., 2017; Mohan et al., 2015; Neuzil et al., 2019). An example of TCV that has been studied is Vi-rEPA (Vi conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A), which was given to 2-5 year old children in two doses with a 6-week interval and showed an estimated efficacy of 89% (Owais et al., 2010; Sahastrabuddhe and Saluja, 2019; Jin et al., 2017; Szu, 2013; Antillón et al., 2017).

Another TCV was Vi-tetanus toxoid (Vi-TT) conjugate vaccine from Bharat Biotech, India whose clinical trial was conducted in United Kingdom (UK). This study showed that Vi-TT is safe and well tolerated, and drastically reduced the number of typhoid cases. The calculated efficacy of Vi-TT was shown to be 54.6% and it is likely that its protective effect in endemic settings is higher (Jin et al., 2017).

The phase I study of a novel Vi-DT (Bio Farma) vaccine was conducted in Jakarta, April 2017 to evaluate the safety and immunogenicity of Vi-DT Typhoid Conjugate Vaccine (Bio Farma) in adults and children above 2 years. One hundred subjects were enrolled in this trial, divided in 2 age groups with 4 arms (2 study and 2 comparator arms), administered two doses of vaccine (4 weeks apart), and followed for 6 months. Serum Anti-Vi IgG was measured before and 4 weeks after first and second dose. The most common local and systemic reactions were pain and muscle pain, respectively. Subjects who received Vi-DT showed a significant increment of GMT ($p < 0.001$) compared to control groups (Vi-PS), both in adults and children groups. All subjects who received Vi-DT showed increasing antibody titer $\geq$4 times following the first and second dosing. The study concluded that Vi-DT TCV is safe and immunogenic for adults and children above 2 years (Medise et al., 2019).

This Phase II study is the continuation of the previously published Phase I study that aims to evaluate the safety and immunogenicity of Vi-DT TCV (Bio Farma) in subjects aged from 6 to <24 months.

Materials and methods

Study design

We conducted a randomized, observer-blind, superiority design of Vi-DT TCV compared to IPV in 6 to <24 months age group. As placebo injection is neither recommended nor considered ethical, and Vi Polysaccharide vaccine is not registered in children under 2 years old, IPV was selected as the control vaccine. Two hundred subjects were enrolled and divided into two groups, control and trial vaccines, with 100 subjects in each group.

Study population

Inclusion criteria were healthy subjects age 6 to <24 months; parents/legal guardians of subjects signed the informed consent form and committed themselves to comply with the instructions and the trial schedule.

Subjects who were involved in another trial, had an axillary temperature above 37.5 °C, had mothers below 18 years, had a known allergy to any component of the vaccines, had a history of blood coagulopathy disorders and those receiving treatment likely to alter the immune response were excluded from the trial. Other exclusion criteria were suffering from a chronic disease that might compromise results and prior receipt of Typhoid vaccine or received any vaccine 4 weeks prior to or following vaccination. Subjects who had previously suffered from typhoid fever at any time and subjects who were planning to move from the study area before the end of the study period were also excluded.

Allocation of participation numbers

After checking inclusion and exclusion criteria, the investigator allocated an inclusion number and randomization code to each subject to decide whether they received control or trial vaccine.

Procedure

Four visits were performed. Visit 1 consisted of blood sampling prior to vaccination, administration of vaccine and evaluation of immediate adverse events post vaccination. Three days post vaccination (Visit 1a) and 7 days post vaccination (Visit 1b) visits consisted of assessment of local and systemic adverse events. On day 28th post vaccination (Visit 2) we performed assessment of local and systemic adverse events as well as blood sampling. Four ml of blood was collected in vacutainer tubes at each visit. Serum samples were separated; samples were stored and shipped to a designated central laboratory at −20 °C to −80 °C.

This study was conducted in the Jatinegara District Primary Health Center, East Jakarta, and Senen District Primary Health Center, Central Jakarta, Indonesia. The subjects were recruited by the research team from the Department of Child Health, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo General National Hospital.

Study intervention

Each dose of the Vi-DT vaccine (0.5 mL) contains a purified Vi capsular polysaccharide of *S. Typhi* (25 μg), 2-phenoxyethanol (preservative) (5 mg), and phosphate buffer solution q.s.0.5 mL. The Vi-DT vaccine was injected intramuscularly in the left anterolateral thigh for subjects aged 6 to 12 months and left deltoid region or left anterolateral thigh for those 12 to <24 months (based on investigator assessment).

The control vaccine used in this trial was inactivated poliomyelitis vaccine which consisted of inactivated poliovirus vaccine type 1 40 Antigen D units, type 2 8 Antigen D units, type 3 32 Antigen D units, 2 phenoxyethanol 2-3 μL and formaldehyde 2-10 μg. It had already been licensed and hence had different packaging shapes and sizes. Therefore, it was not possible to use blinded labels to implement the double-blind procedure. In order to take care of the situation, an unblinded team was appointed to handle and administer vaccines.

Safety and immunogenicity evaluation

Safety data were collected 30 min, 3 days, 7 days and 28 days post vaccination. We recorded all local and systemic, immediate and delayed reactions. Reports for the same were routinely reviewed by the Data Safety Monitoring Board (DSMB).

Antibody titers were evaluated by ELISA. The assay was performed by Clinical Trial Laboratory of Bio Farma in a blinded fashion. The procedure was validated and approved by the Quality Assurance of Bio Farma. ELISA used in this study used a new standard, established by the WHO Expert Committee on Biological Standardization, NIBSC 16/138 as the first International Standard (IS) for anti-Vi IgG with 100 IU per ampoule, where this Clinical Trial Laboratory of Bio Farma also contributed in this collaborative study to established this IS standard for anti-Vi IgG (Rijpkemaa et al., 2018).

Sample size and data analysis

By assuming a maximum seroconversion rate among controls as 0.7, if the true seroconversion rate for Vi-DT vaccine subjects is 0.9, the study needed 82 Vi-DT subjects and 82 control subjects to be able to reject the null hypothesis that the seroconversion rates for experimental and control subjects are equal with probability (power) of 0.9. Assuming 20% dropout rate and issues related to inadequate samples, it was planned to enroll 100 subjects in each group.

The seroconversion rates post vaccination and the GMT with their 95% CIs were described at V2. A four-fold increase of titer from the baseline value was considered as the measure of seroconversion. The randomization code was opened after the laboratory officially released the test results to the investigators.

Vaccine safety was analyzed by computing the number and percentage of any adverse events experienced by subjects. All data were analyzed using SPSS 20.

Results

Two hundred subjects were recruited from the month of July up to December and were followed up to 28 days post vaccination. All subjects were healthy prior to vaccination based on physical examination by a pediatrician. Out of the 200 subjects that took part in the study, the number of males and females were roughly the same. The control group had 50 males and 50 females whereas the Vi-DT group had 47 females and 53 males. The mean age of the subjects was 14.73 months for control group and 14.14 for Vi-DT group. Up to 28 days post vaccination, there were 2 dropouts (1%) due to family reasons. The study flow can be seen in Figure 1.

Safety evaluation

The immediate and delayed adverse events post vaccination are described in Table 1. Overall, both control and Vi-DT arms showed similar safety outcomes, however there were a few that revealed a significant difference between control and Vi-DT groups. The Vi-DT group showed higher incidence of local immediate reactions and within 24 h post vaccination compared to the control group (as shown in Table 1). Pain was the most common immediate local reaction followed by redness. Swelling and induration were also found in small amounts in the Vi-DT group only. Fever was the most common immediate and delayed systemic reaction followed by muscle pain. Few cases of irritability and fatigue were also found in both Vi-DT and control groups (Table 2). All local and systemic reactions that occurred 30 min post vaccination were mild to moderate in intensity. Most reactions that occurred > 30 min were also mild to moderate except for fever with temperatures above

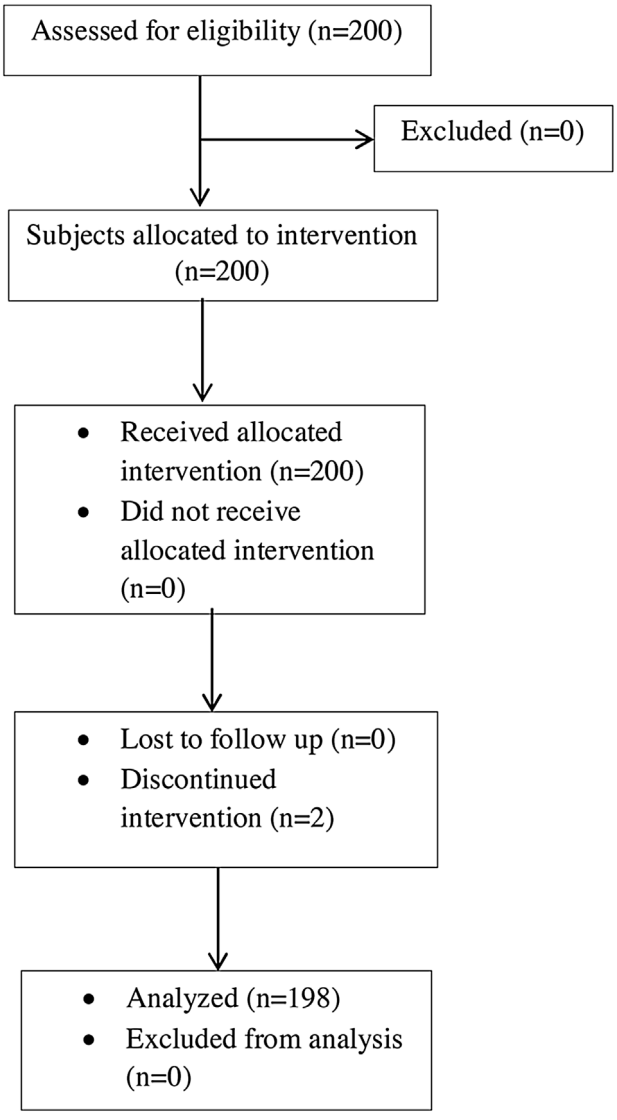

Figure 1. Study flowchart.

Table 1
Immediate and delayed reactions.

Description	Vi-DT, n (%)	Control, n (%)	P
Any immediate reaction			
any immediate local reaction	9(9%)	1(1%)	0.009*
any immediate systemic event	6(6%)	1(1%)	0.118
Any delayed adverse event 31 min–24 h			
any delayed local reaction	8(8%)	0	0.004*
any delayed systemic event	22(22%)	14(14%)	0.140
Any delayed adverse event 24–48 h			
any delayed local reaction	1(1%)	0	1
any delayed systemic event	4(4%)	1(1%)	0.368
Any delayed adverse event 48–72 h			
any delayed local reaction	0	0	1
any delayed systemic event	3(3%)	1(1%)	0.621
Any delayed adverse event 72 h– 7 days			
any delayed local reaction	0	0	1
any delayed systemic event	13(13%)	16(16%)	0.688
Any delayed adverse event 8 28 days			
any delayed local reaction	0	0	1
any delayed systemic event	35(35%)	28(28%)	0.285

* $p < 0.05$ indicates significant difference.

39° (Table 3). Most of the adverse events lasted no more than 48 h. There were no serious adverse events within 28 days post vaccination.

Although the two vaccines are different, the local and systemic reactions that arise are generally not significantly different.

Immunogenicity evaluation

Antibody titer was measured 28 days post vaccination and compared to the baseline. Seroconversion rate was 98.99% for Vi-DT and 3.03% for control Figure 2 shows the percentage of subjects with increasing antibody titer 28 days post vaccination. Table 4 shows GMT of antibody following immunization. The GMTs in Vi-DT group induced significantly higher antibody compared to the control group ($p < 0.001$).

Almost 100% of infants and children who received the typhoid Vi-DT vaccine had antibody increment of >4 times.

Discussion

Typhoid and paratyphoid are among the most common bacterial causes of morbidity worldwide, especially in low- and middle-income countries (Saha et al., 2019). The global incidence of typhoid in 2000 was an estimated 21,650,974 cases with 216,510 deaths and it is still a major cause of illness today (Brooks et al., 2005). Current estimates show that each year there are 12 million cases and over 128 000 deaths attributed to typhoid, with children and adolescents ages 2-15 years being the most affected age group. The highest incidence was reported in Asia and Africa (Jamka et al., 2019; Crump et al., 2004; Ochiai et al., 2008; Alba et al., 2016).

In our previous phase I study of this novel Bio Farma Vi-DT vaccine, we used a two-dose vaccination with a month interval. Our previous study revealed that this vaccine is safe and immunogenic in adults and children older than two years. It was also proven that a single dose of the vaccine was sufficient to induce seroconversion and high GMT in all subjects aged above 2 years old (Medise et al., 2019). Based on our previous results, we decided to test the safety and immunogenicity in children 6 to <24 months and give only one dose vaccination.

All subjects participated in visit 1, Visit 1a (+3 days after vaccination) and Visit 1b (+7 days after vaccination). There was a total of two dropouts due to family reasons. Therefore, at visit 2 there were 198 (99%) subjects who still continued the study.

Our study showed that the seroconversion of Vi-DT vaccine was 98.99% and only 3.03% in the control group. Four weeks after vaccination, the GMT was significantly higher for those who received the Vi-DT vaccine than those who received control. (Table 4).

A double blind randomized controlled trial was conducted in India to evaluate the safety and immunogenicity of a Typhoid conjugate vaccine. This study involved subjects aged 6-23 months who received a single dose of Typhoid Vi polysaccharide- tetanus toxoid conjugate vaccine in an open label trial. The study showed that at day 42, TCV was found to be highly immunogenic with seroconversion (>4-fold rise over baseline) as 98.1%, GMT 1937 EU/mL, and confidence interval 1785-2103 (Mohan et al., 2015). Our results are comparable to these results in India.

Our study area was in a slum, urban area of Central and East Jakarta city, which are parts of a downstream area in the North part of Java Island. Previous study showed that cases of typhoid fever among children tended to be concentrated in downstream areas (Akullian et al., 2015).

In our study, both control and Vi-DT arms showed similar safety outcomes, except for a few cases where the difference was significant. The immediate local reaction (30 min post vaccination) for Vi-DT showed higher local reaction compared to the control group with p = 0.009. The delayed local reaction (31 min to 24 h) for the Vi-DT group was also higher than that of control with p = 0.004 (Table 1). However, the severity of most of the local reactions was mild to moderate. Most of the local reactions resolved within 48 h post vaccination. For systemic reactions, both control and Vi-DT groups showed similar safety outcomes, with no significant difference between the two groups. Many delayed systemic reactions were found 8 days to 28 days post vaccination. However, most of the systemic reactions were caused by other diseases such as upper respiratory tract infections, gastroenteritis, viral

Table 2
Local and systemic reactions up to 24 h post vaccination.

Description	30 min post vaccination			31 min to 24 h post vaccination		
	Vi-DT	Control	p	Vi-DT	Control	p
Pain	5%	0	0.059	6%	0	0.028
Redness	2%	1%	1	0	0	–
Swelling	1%	0	1	1%	0	1
Induration	1%	0	1	1%	0	1
Other local reactions	0	0	–	0	0	–
Fever	2%	0	0.786	10%	7%	0.466
Fatigue	2%	0	0.786	5%	2%	0.248
Muscle pain	2%	1%	0.854	4%	3%	0.976
Irritability	0	0	–	2%	1%	0.858
Other systemic reactions	0	0	–	1%	1%	1

Table 3
Intensity of local and systemic reactions from 30 min to 28 days post vaccination.

Description	Intensity																	
	Within 30 min						p	31 min to 72 h						p	72 h to 28 days						P
	Vi-DT			Control				Vi-DT			Control				Vi-DT			Control			
	Mild	Moderate	Severe	Mild	Moderate	Severe		Mild	Moderate	Severe	Mild	Moderate	Severe		Mild	Moderate	Severe	Mild	Moderate	Severe	
Local reaction																					
Pain	5	0	0	0	0	0	0.059	6	1	0	0	0	0	0.028	0	0	0	0	0	0	-
Redness	2	0	0	1	0	0	1	0	0	0	0	0	0	-	0	0	0	0	0	0	-
Swelling	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	-
Induration	1	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	-
Other	0	0	0	0	0	0	-	0	0	0	0	0	0	-	0	0	0	0	0	0	-
Systemic event																					
Fever	1	0	0	0	0	0	1	7	2	3	6	2	0	0.345	10	9	4	9	6	8	1
Fatigue	2	0	0	0	0	0	0.497	4	2	0	2	0	0	0.279	3	2	0	2	1	0	0.470
Muscle pain	2	0	0	1	0	0	0.497	3	0	1	3	0	0	1	1	0	0	0	1	0	1
Irritability	0	0	0	0	0	0	-	2	1	0	1	0	0	0.621	2	0	0	3	1	0	0.682
Other	0	0	0	0	0	0	-	2	0	0	1	1	0	1	15	0	1	4	3	1	0.081

Although the two vaccines are different, the local and systemic reactions that arise are generally not significantly different.

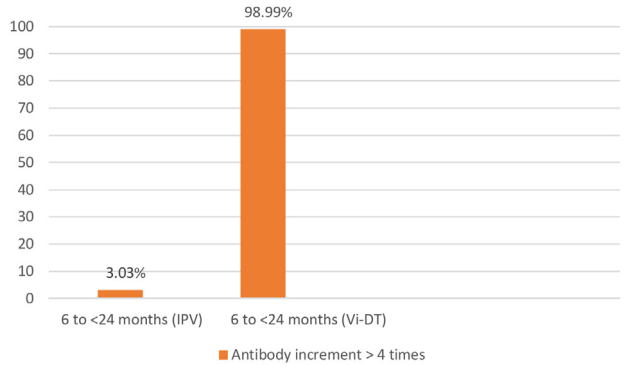

Figure 2. Percentage of subjects with increasing antibody increment >4 times 28 days post vaccination.

Table 4
Geometric mean titer (GMT) of antibody following immunization.

Group	GMT V1 (95%CI) Pre Immunization (IU/mL)	p	GMT V2 (95%CI) 28 days post immunization (IU/mL)	P
Vi-DT	0.00001217	0.099	301.5489	<0.001
Control	0.0000034		0.0000037	

infections etc. not related to vaccination.

Some reactions were found to be higher in the Vi-DT group compared to IPV because the type as well as compositions of the two vaccines are different. Hence, IPV is not a fair comparison to our trial vaccine. No typhoid conjugate vaccine has been registered in Indonesia to be used as a control vaccine. The purpose of using IPV in this trial is to prevent a biased analysis and eliminate the need to use a placebo. The investigators decided not to use a placebo because of ethical considerations.

A Phase II trial was conducted in Philippines to evaluate the safety, immunogenicity and reactogenicity of Vi-DT typhoid conjugate vaccine in children 6-23 months. No comparator vaccine was used, instead, placebo was given to those who did not receive the trial vaccine. Safety data was collected 60 min, 7 days and 28 days post vaccination. In this trial, pain and tenderness were the most common local reactions whereas fever was the most common systemic reaction. There was no statistical difference in adverse events between trial vaccine and placebo. Most of the adverse events were of mild to moderate severity except for one case of severe fever. One severe adverse event occurred in the Vi-DT group with a diagnosis of febrile convulsion due to urinary tract infection. This adverse event was unrelated to the vaccination (Capeding et al., 2019). Our study showed similar results where pain was also the most common immediate reaction in both groups, test and control vaccines. However, in our study, pain was found to be higher in Vi-DT group compared to control group (Table 2). Fever was also the most common systemic reaction, with slightly higher numbers found in the Vi-DT group.

Our study is similar to the study in Philippines (Capeding et al., 2018; Capeding et al., 2019) in regard to the severity of local and systemic reactions. Most of the severity of immediate and delayed reactions was found to be mild to moderate except for fever with temperatures above 39 °C (Table 3). These however lasted no more than 24 h, resolved without sequelae and were deemed unrelated to the vaccination. We found no serious adverse events within 28 days after vaccination.

Conclusions

Our phase II study concluded that the typhoid conjugate Vi-DT vaccine is safe and immunogenic in children 6 to <24 months.

Conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

Financial disclosure

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Contributors' statement

Bernie Endyarni Medise, dr., SpA(K), MPH conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Prof. Dr. Soedjatmiko Soedjatmiko, dr., SpA(K), M.Si, Dr. Hartono Gunardi, dr., SpA(K), Prof. Dr. Rini Sekartini, dr., SpA(K), Prof. Dr. Hindra Irawan Satari, dr., SpA(K), M.TroPaed, Prof. Dr. Sri Rezeki Hadinegoro, dr., SpA(K), dr. Angga Wirahmadi, SpA coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr. Novilia Sjafri Bachtiar, dr., M.Kes, Rini Mulia Sari, dr.,M.Kes., Mita Puspita, dr., designed the study and the data collection instruments, analyzed blood sample, provided vaccine, critically reviewed the manuscript, and approved the final manuscript as submitted.

Jae Seung Yang, Arijit Sil, Sushant Sahastrabuddhe reviewed design of the study and critically reviewed the manuscript.

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