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Immunogenicity and safety of a Trivalent Influenza HA vaccine in Indonesian infants and children

Soedjatmiko Soedjatmiko [a], Bernie Endyarni Medise [a,*], Hartono Gunardi [a], Rini Sekartini [a], Hindra Irawan Satari [a], Sri Rezeki Hadinegoro [a], Novilia Sjafri Bachtiar [b], Rini Mulia Sari [b]

[a] Department of Child Health, Faculty of Medicine, Universitas Indonesia, Jalan Salemba 6, Jakarta 10340, Indonesia
[b] PT. Bio Farma, Jalan Pasteur 28, Bandung 40161, Indonesia

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ABSTRACT

Introduction: High rate of influenza infection in children made influenza vaccination strongly recommended for all person aged >6 months in Indonesia. Bio Farma Trivalent Influenza HA (Flubio®) vaccine has been used in adolescents and adults, resulted in increased seroconversion, seroprotection rates and geometric mean titer (GMT). However, no data is available regarding its efficacy and safety in children. This study aimed to assess the immunogenicity and safety of Flubio® vaccine in infants and children.

Materials and methods: This was a phase II, open-labeled, clinical trial conducted on healthy children aged 6 month-11 years, vaccinated with 1 or 2 doses of Influenza HA vaccine, with a 28-day interval. Flubio® vaccine composed of A/California/7/2009 (H1N1) pandemic 09, A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 strain. This study was held at East Jakarta, Indonesia from May until July 2014. A Total of 405 subjects were included and divided into three groups: A(6–35 months), B(3–8 years), and C(9–11 years). Antibody titer was measured at visit V1 (Day 0), V2 (28 days/+7days after the first dose) and V3 (28 days/+7days after second dose). The seroprotection and seroconversion rates were assessed. Safety was assessed up to 28 days following each dose.

Results: A total of 404 subjects completed the study. After vaccination, all subjects achieved seroprotection and increased seroconversion rates, with post-vaccination antibody titer of ≥1:40 HI for all strains. The GMT also increased significantly. Within 30 min after vaccination, 14.6% and 2% had local and systemic reactions; meanwhile, between 30 min to 72 h after vaccination, 35.1% and 13.6% subjects had local and systemic reactions, respectively. Most reactions were mild. No serious adverse event (SAE) was reported related to vaccine.

Conclusion: Flubio® (Influenza HA Trivalent) vaccine is immunogenic and safe for children aged 6 mont hs-11 years.

Trial Registration: The trial is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02093260.

1. Introduction

Immunization is the most cost-effective health innovation and investment, effective in reducing illness and death from infectious diseases, including influenza [1,2]. Influenza viruses, especially type A and B, cause considerable mortality and morbidity every year, and may cause seasonal influenza outbreaks, epidemics and pandemics [3]. Influenza viruses are common in global circulation and occur throughout the year with one or two peaks [4,5]. Globally, 600 million cases and 250–500 thousand deaths are linked to influenza annually [6,7].

Influenza vaccine has shown more benefits when given to high-risk individuals, especially children. The highest rates of influenza infection occur in children aged less than 5 years, particularly in those less than 2 years [6,7]. In 2008, there were 90 million new cases of seasonal influenza, and contributed 28,000–111,500 deaths [8]. In developing countries, the highest infection rates are found in children aged 5–9 years with serious morbidity and mortality occur most frequently in children under 2 years [9,10]. A study in children below 14 years in East Jakarta with influenza like illness (ILI) and pneumonia showed that prevalence of influenza A and B was 8.3%, in which influenza B virus was dominant.

* Corresponding author.
E-mail address: bernie.medise@yahoo.com (B.E. Medise).

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The prevalence of influenza in this area was higher in children older than 5 years compared to younger age [9]. The American Academy of Pediatrics (AAP) and the Indonesian Pediatric Society (IPS) recommend annual seasonal influenza vaccination for everyone aged 6 months and older. Influenza vaccination is necessary not only for older children, but also for the young infants [11,12].

Influenza cases in Indonesia were dominantly caused by influenza A(H1N1) [10,13]. Moreover, updated data from World Health Organization (WHO) in 2015 showed that the most common circulating influenza A viruses were influenza A(H1N1) and influenza A(H3N2) subtypes [5]. These facts enhanced the influenza vaccine containing type A and B as part of strategies for illness prevention.

Even though influenza vaccination has been widely used, its efficacy and safety in children still needs further study. From previous studies in Indonesian adolescents aged 12–18 years and adults, Bio Farma Influenza HA vaccine (Flubio®) was immunogenic, well-tolerated and had no serious adverse event (SAE) [12,14,15]. Flubio® has become the first licensed product of WHO technology transfer initiative in 2009 [16]. Studies in children indicate that administration of influenza vaccination is safe and able to produce desired immunogenicity. The immune response against influenza vaccine in children was highly influenced by pre-vaccination antibody levels and age [17,18]. Eventhough IPS immunization schedule has recommended influenza HA vaccination starting at 6 month old, Flubio®, as National product, has not been used for Indonesian children since there are no data about its immunogenicity and safety in infants and children under 11 years old. Therefore, this study aimed to determine the immunogenicity and safety of Flubio® vaccine in infants and children.

2. Materials and methods

2.1. Study design

This was a phase II clinical trial, open-labeled study to assess immunogenicity and safety of Flubio® vaccine in infants and children. It was approved by Research Ethics Boards of Faculty of Medicine, Universitas Indonesia and registered at US National Institutes of Health (ClinicalTrials.gov) # NCT02093260.

2.2. Study population

Four hundred and five infants or children were divided into three age groups: A(6–35 months), B(3–8 years), and C(9–11 years). Inclusion criteria were healthy infants and children aged 6 months to 11 years, parents were informed properly, signed consent form, and committed themselves to comply the instructions and trial schedule. Subjects having mild, moderate or severe illness, with temperature ≥37.5 °C were excluded. Other exclusion criteria were history of allergy to egg, chicken protein or vaccine component, history of uncontrolled hematologic disorders contraindicating intramuscular injection, history of medications that might alter immune response in the previous 4 weeks, any abnormality or chronic diseases that might interfere with assessment of trial objectives, and individuals immunized with influenza vaccine within last one year, or any vaccination within one month prior to and subsequent to immunization of Influenza HA vaccine.

Subjects were recruited by research team from Cipto Mangunkusumo Hospital/Department of Child Health, Faculty of Medicine, Universitas Indonesia from Jatinegara District Primary Health Center (PHC) area and primary school of SDN 01 Kampung Melayu, Eastern part of Special Capital Region of Jakarta, Indonesia, where study was held from May until July 2014.

2.3. Allocation of participant numbers

Inclusion number was allocated in the chronological order for subject that was included in the trial from 001 to 405. Each subject received one code according to the age group.

2.4. Study intervention

Influenza HA vaccine is formulated in Bio Farma with lot number 3020213. Each 0.5ml Flubio® composed of 15 μg HA of each strain (A/California/7/2009(H1N1)pdm09, A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012), and 4 μg thimerosal. Vaccine was stored at a temperature ranging from 2 °C to 8 °C. Vaccine was given to each subject intramuscularly at left antero lateral thigh region for subjects ≤2 years or left deltoid region for subjects >2 years using 22–25-gauge needle. Group A received 2 doses (0.25 ml), group B received 2 doses (0.5 ml) and group C received 1 dose (0.5 ml) of Flubio® vaccine. The interval between 2 doses vaccine was 28–35 days.

Four milliliters of blood was collected in vacutainer tubes for all groups prior to vaccination, at visit 2(V2) for group C, and at V3 for group A and B. All blood samples were labeled and stored at −20 °C to −80 °C. Antibody titers were measured by using Hemagglutination Inhibition(HI) test performed in Immunology Laboratory of Clinical Trial Department of Bio Farma. This HI method had been validated and approved by Quality Assurance Division [19].

2.5. Study outcomes

We assess immunogenicity of Influenza HA vaccine by calculating percentage of subjects with anti-influenza titer ≥1:40 HI units or seroconversion rates, seroprotection, and the increment of GMT post vaccination.

Subjects were provided with thermometer and instruction on how to use it, and observation cards (diaries) to record information for local/systemic reactions within 28 days following each immunization. Diary cards were collected at the visit to clinic, home visit by field visitors, or by calling the parents. Any SAE occurs during the trial period should be reported immediately and recorded in Case Report Form (CRF).

2.6. Sample size and study analysis

We estimated a total of 323 subjects needed, with $\alpha = 0.05$ and value of anticipated population proportion is 0.70. Estimation of loss-to-follow up subjects are 25%, resulted in 404 subjects as minimum required subjects.

Vaccine safety was analyzed by computing number and percentage of local and systemic reaction experienced by subjects. All analysis were conducted using SPSS.20.

3. Results

There were 135 subjects enrolled in each group A, B, and C. Only one subject (group A) was dropped out because the parents refused to continue the study. The study flow can be seen in Fig. 1.

Characteristics of subjects and seroprotection rate of vaccine (anti Influenza titer >1:40 HI) 28 days after immunization is shown in Table 1. Seroprotection rate was 100% for all three strains after immunization.

Differences of GMT increment pre- and 28/+7 days post-immunization among groups A, B, and C was significant ($p < 0.00$ 01) for the three strains (Fig. 2). Post-immunization GMT increment was significant for A(H1N1) (CI 95% 1044.36–1254.65;

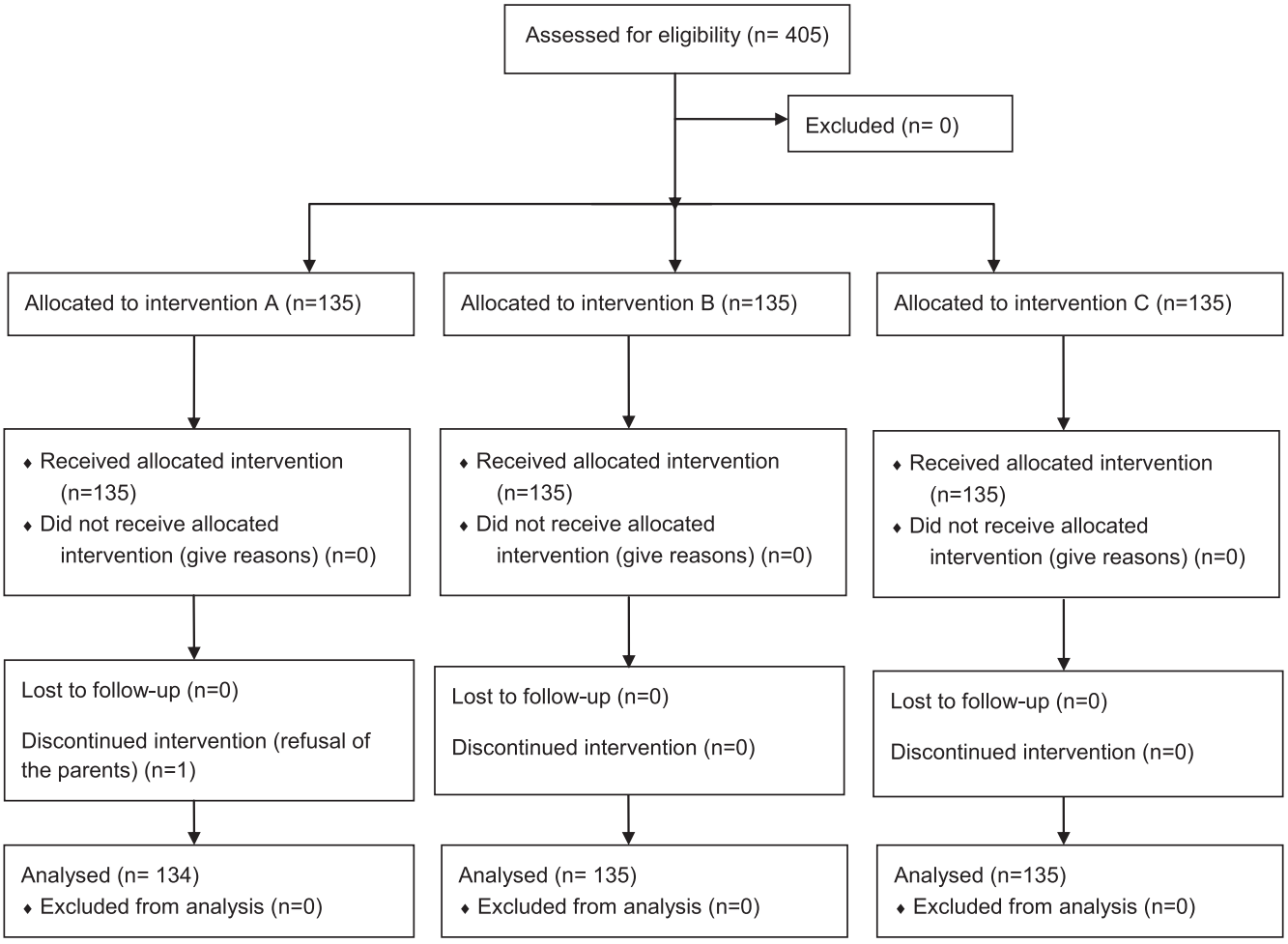

Fig. 1. Flow chart of the study.

Table 1
Influenza HA vaccine subject characteristics and seroprotection rate pre- and 28 days post-immunization.

Description	Group A (n)		Group B (n)		Group C (n)		All (n)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
	135	134	135	135	135	135	405	404
Gender								
Male n (%)	72 (53.3)	71 (52.9)	76 (56.2)	76 (56.2)	63 (46.7)	63 (46.7)	211 (52.1)	210 (52)
Female n (%)	63 (46.7)	63 (47.1)	59 (43.7)	59 (43.7)	72 (53.3)	72 (53.3)	194 (47.9)	194 (48)
Age (Months)								
Mean + SD	22.08 ± 8.57	22.02 ± 8.57	73.59 ± 22.66	73.59 ± 22.66	123.11 ± 13.64	123.11 ± 13.64	73.73 ± 44.42	73.03 ± 44.29
Min; max	6.48; 35.00	6.48; 35.00	36.00; 107.00	36.00; 107.00	37.00; 147.12	37.00; 147.12	6.48; 147.12	6.48; 147.12
A/California/7/2009 (H1N1)								
<1:40 HI, n (%)	10(7.4)	0(0)	3(2.2)	0(0)	4(3)	0(0)	17(4.2)	0(0)
≥1:40 HI, n (%)	125 (92.6)	134(1 0 0)	132(97.8)	135(1 0 0)	131(97)	135(1 0 0)	388(95.8)	404(1 0 0)
A/Texas/50/2012 (H3N2)								
<1:40 HI, n (%)	3(2.2)	0(0)	3(2.2)	0(0)	0(0)	0(0)	6(1.5)	0(0)
≥1:40 HI, n (%)	132(97.8)	134(1 0 0)	132(97.8)	135(1 0 0)	135(1 0 0)	135(1 0 0)	399(98.5)	404(1 0 0)
B/Massachusetts/2/2012								
<1:40 HI, n (%)	11(8.1)	0(0)	10(7.4)	0(0)	2(1.5)	0(0)	23(5.7)	0(0)
≥1:40 HI, n (%)	124(91.9)	134(1 0 0)	125(92.6)	135(1 0 0)	133(98.5)	135(1 0 0)	382(94.3)	404(1 0 0)

$p < 0.001$), A(H3N2) (CI 95% 572.31–693.83; $p < 0.001$), and B (CI 95% 724.86–880.49; $p < 0.001$).

There were significant differences among group A, B and C in terms of percentage of subjects with >4 times increment of anti-Influenza HA titer in 28 days post-immunization of each strain ($p < 0.001$ for each group) (Table 2).

The adverse event(AE) are described in Tables 3 and 4. In this study, there were 24 other types of delayed systemic events (72 h to 28 days) reported. These AE were 2 measles cases, 12 viral exanthema cases, one varicella zoster, 6 diarrhea cases, one mumps case, one Bell's palsy, and one stomatitis event. There was one subject with SAE who needed hospitalization was

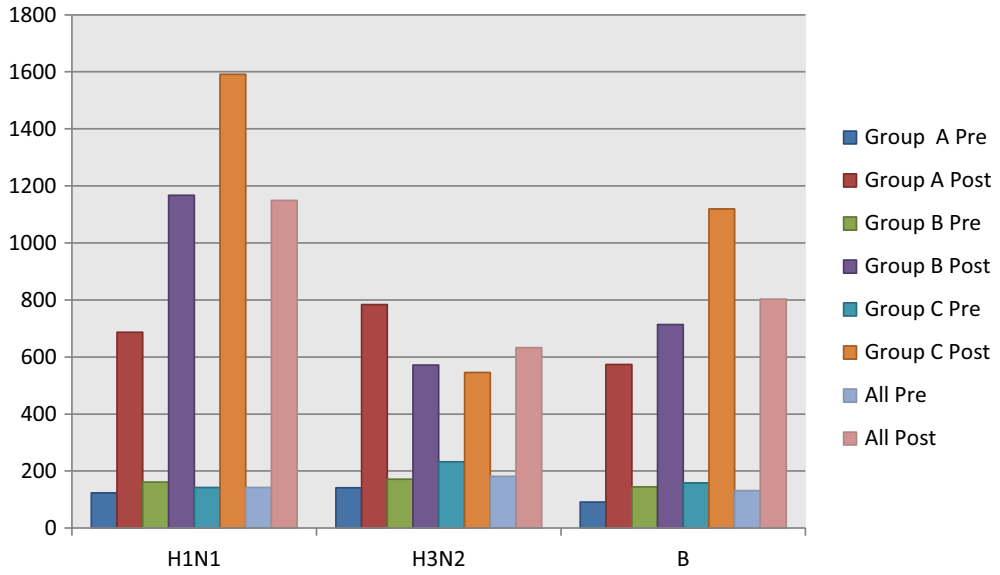

Fig. 2. Pre- and 28 days post-immunization Geometric Mean Titers (GMT) to influenza A (H1N1), A (H3N2), and B virus strains.

Table 2
Percentage of subjects with ≥4 times increment of antibody titer in 28 days post-immunization.

Description	Group A (n)	Group B (n)	Group C (n)	All (n)
	134	135	135	404
	n (%)	n (%)	n (%)	n (%)
A/California/7/2009 (H1N1)	85(63.4)	110(81.5)	112(90.4)	317(78.5)
A/Texas/50/2012 (H3N2)	90(67.2)	71(52.6)	49(36.3)	210(52)
B/Massachusetts/2/2012	90(67.2)	101(74.8)	104(77)	295(73)

Table 3
Percentage of types and intensity of related local and systemic adverse events occurred within 30 min post-immunization.

Description	Intensity n (%)		
	Mild	Moderate	Severe
Local (at least one reaction)			
Pain	18 (4.4)	0 (0)	0 (0)
Redness	33 (8.1)	1 (0.2)	0 (0)
Swelling	4 (0.9)	0 (0)	0 (0)
Induration	4 (0.9)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Systemic			
Fever	1 (0.2)	0 (0)	0 (0)
Fatigue	1 (0.2)	0 (0)	0 (0)
Muscle pain	5 (1.2)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)

diagnosed with dengue hemorrhagic fever and classified as unrelated to vaccination.

4. Discussion

This study aimed to determine immunogenicity and safety of Flubio® vaccine in children aged 6 months – 11 years. Previous study in Indonesian adolescents aged 12–18 years showed majority of subjects experienced seroconversion and 10 times increased of post vaccination GMT [12]. In our study, there were no differences in percentage of subjects with seroprotection post immunization. This may be due to most subjects have already had antibody for influenza virus prior to vaccination. More than 90% subjects had antibody titer ≥1:40 prior to vaccination (Table 1). Moreover, administration of influenza vaccine was able to cause a significant increase in the GMT of subjects. Administration of vaccine, despite prior exposure to infection, still proved to be beneficial for children. There may be several reasons that underlie this justification. Firstly, though achievement of antibody titer of ≥1:40 is associated with a significant reduction of influenza incidence, higher titer level provides higher protection against infection [20]. Hence, administration of influenza vaccine for person with antibody titer of ≥1:40 is justifiable. Secondly, previous studies showed that occurrence of influenza increases within one influenza season, so that vaccine may still be given to provide longer protection against infection [8].

Surveillance data from East Jakarta revealed that influenza type B and subtype A(H1N1), and A(H3N2) viruses were the most frequently reported [21]. Moreover, several studies have reported that influenza occurs in 6–29.7% infants and children in Indonesia annually, indicating that occurrence of influenza infection in Indonesia is high [10,22,23]. As a result, regular influenza vaccinations as an effort to prevent infection should be considered. Influenza (HA) vaccination has been recommended also for children >6 months old in developed countries like USA and United Kingdom. As the follow-up, these vaccinations are able to provide protection against influenza and complications [24,25]. Therefore, the IPS immunization schedule also recommends influenza vaccination for children [12,26].

In our study, antibody titer of <1:40 prior immunization was mostly found in group A (below 3 years), followed by group B (3–8 years), then C (>9 years old). Antibody titer of ≥1:40 for strain A(H3N2) reached 100% in group C prior to vaccination (Table 1). This finding indicates that younger subjects are at higher risk of influenza compared to older children, highlighting the necessity of influenza vaccinations for children less than 3 years. Similar results have been reported by other study in Indonesia [10]. Several other studies have reported benefits of influenza vaccinations for children, including decreased incidence and its complications [7,25,27,28]. The vaccination is also able to induce immunity in children, both humoral and cell-mediated, beyond influenza season [29]. Our study strengthened the need to give influenza vaccinations at earlier age.

Table 4
Summary of adverse events.

Description	Group A		Group B		Group C		All		*p*
	n	%	n	%	N	%	n	%	
Any immediate reaction (from 0 to 30 min post immunization)									
Any immediate local reaction	41	30.4	11	8.1	7	5.2	59	14.6	0.118
Any immediate systemic event	4	3	1	0.7	3	2.2	8	2	
Any delayed adverse event (from 31 min to 72 h post immunization)									
Any delayed local reaction	75	60	42	31.1	25	18.5	142	35.1	0.44
Any delayed systemic event	26	19.4	21	15.6	8	6	55	13.6	
Any delayed adverse event (from 72 h to 28 days post immunization)									
Any delayed local reaction	0	0	0	0	0	0	0	0	[a]
Any delayed systemic event	75	56	56	41.5	11	8.1	142	35.1	

Group A: 6 months – 35 months old.
Group B: 3–8 years old.
Group C: 9–11 years old.
[a] Can't be computed because variable is constant.

In this study, the highest GMT increment was observed in group C for strain A(H1N1) which was 10 times. However, the lowest GMT increment was also found in this subject group for A(H3N2) (1.3 times) (Fig. 2). Post-immunization GMT of all strains increased significantly ($p < 0.001$). This is similar to previous study on adolescents using Flubio® conducted in Bandung, Indonesia, which showed that post-immunization GMT increased for all strains: A/Brisbane/59/2007(H1N1) (76.4–992.7 HI units), A/Uruguay/716/2007 (H3N2) (27.6–432.1 HI units), and B/Brisbane/60/2008 (19.9–312.7 HI units). After 28 days of immunization, antibody titers had increased by ≥4 times in 75.8%, 84.5% and 77.6% of subjects for A(H1N1), A(H3N2), and B/Brisbane, respectively [15].

Our study revealed that despite the high seroprotection rate, the percentage of subjects with ≥4 times increment of antibody titer in each group was not high. One month after receiving two shots of Flubio® vaccine, percentage of children aged 6–35 months with ≥4 times increment of antibody titer were higher than before immunization for all strains. Percentage of children aged 36 months – 8 years with >4 times increment of antibody titer is higher compared to younger subjects in two strains. In contrary, after immunization, percentage of children 9–11 years with antibody titer of A(H3N2) only increased by 36.3% (Table 2). This may be due to the fact that among older children, pre-immunization GMT of Anti Influenza HA vaccine level for A(H3N2) strain was the highest, while post-immunization GMT level for A(H3N2) strain was the lowest among other groups and strains (Fig. 2). However, the ≥4 times increment of antibody titer in 28 days after immunization were significantly different for each strain ($p < 0.001$). In general, among all subject groups, children below 3 years had the lowest pre- and post-immunization GMT. These support the fact that immunity in children is not as high as in adolescent and adult because of immature immunity function due to age [18,19].

One household study conducted in children during 2012–2013 season reported that there was no significant influenza vaccine effectiveness in children below 9 years, which highlights the possibility that administration of vaccine at a younger age may not be beneficial [30]. It must be noted that this study was done at a different time period and study parameters, such as subject age group. Therefore, administration of vaccine should still be considered for younger children as shown in our and other studies. Furthermore, many studies have shown benefits of influenza vaccine in reducing prevalence of infection [7,11,23,28]. Also, the presence of contradicting results highlights the necessity of conducting regular surveillance on the actual effects brought by influenza vaccinations, considering continuous drift of influenza virus which may circumvent immunity [11,16,24,30].

Another study in toddlers shows the importance of assessment of immune responses in children after alteration in vaccine composition. This is due to the fact that influenza vaccines change frequently, affecting not only antibody responses in partially immunized toddlers, but potentially immune responses in more fully immunized individuals. Therefore, we need to consider the importance for giving multiple doses of vaccine to produce potentially protective antibody levels in children [31].

It must be noted that despite previous exposure to influenza viruses, there is a great deal of evidence which show previous infection enhanced immunogenicity of vaccination, especially in older children [32]. Therefore, influenza vaccination should not only be considered for younger children as older patients will experience benefits from vaccine administration.

Our study showed that within 30 min following immunization, most of immediate AE were mild and local reactions [Table 3]. The delayed systemic event between 31 min to 72 h post immunization among groups were not different. However, younger subjects experienced more AE compared to older subjects [Table 4]. Our result [Table 3] is similar with other studies in children, that the most common injection site adverse reactions were pain, redness, and swelling. While the most common systemic AE after influenza vaccination in children were drowsiness, irritability, loss of appetite, fatigue, and muscle aches [11]. Another study revealed that the most common reaction among 6–24 months were irritability and injection-site tenderness, whereas among 2–9 years were myalgia, malaise, and injection-site pain [33].

Other types of delayed systemic events in our study have no correlations with vaccination, except for Bell's palsy and a couple of viral exanthema cases. These AE were classified as probable based on causality assessment. The association between influenza vaccine and Bell's palsy has not been concluded [34–37]. However, other studies suggest the correlation between Bell's palsy and influenza vaccine [38,39]. Therefore, further study is required.

There are several limitations of this study. Subjects were recruited only from one area that was considered as a slum area, thus lacking a comparison to those living in more decent areas. This should be taken into consideration as there may be differences between both areas which may affect occurrence and transmission of influenza. In addition, there was no placebo group as comparison used in this study, thus direct comparison to patients who do not receive the vaccine cannot be made. Further studies are needed.

In conclusion, Flubio® (Influenza HA Trivalent) vaccine is immunogenic and safe for children aged 6 months up to 11 years, with limited side effects and no vaccine-related SAE. In addition, after receiving Influenza HA vaccine, all subjects were seropositive against all strains of influenza virus.

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Conflict of Interest

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

Contributors' Statement

Dr. Soedjatmiko Soedjatmiko, dr., SpA (K), M.Si conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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

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

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