Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 26 February 2018
Accepted 28 February 2018
Available online xxxx

Keywords:
Children
Efficacy
Immunogenicity
Infant
Influenza vaccine
Safety

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 $\geq$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.

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https://doi.org/10.1016/j.vaccine.2018.02.114
0264-410X/

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 $\geq$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 $\leq$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 $\geq$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;

Please cite this article in press as: Soedjatmiko S et al. Immunogenicity and safety of a Trivalent Influenza HA vaccine in Indonesian infants and children. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.114