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# Clinical testing of an inactivated influenza A/H5N1 vaccine candidate in a double-blinded, placebo-controlled, randomized trial in healthy adults in Vietnam ☆

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ABSTRACT

We tested an inactivated egg-grown whole virus influenza A/H5N1 vaccine candidate developed by the Institute of Vaccines and Medical Biologicals (IVAC), a state-run vaccine manufacturer in Vietnam, in a Phase 1, placebo controlled, double blinded, randomized trial. The vaccine was adjuvanted with aluminum hydroxide. The trial enrolled 75 subjects who were randomized to receive two injections of one of the following: low-dose of vaccine (7.5 mcg HA), high-dose of vaccine (15 mcg HA), or placebo. The vaccine candidate was well tolerated with minimal local reactogenicity consisting of mild, short-lived injection site pain and/or tenderness. No systemic reactogenicity was observed other than transient low-grade fever in about 13% of the subjects and no unsolicited adverse events were attributable to product administration. Immune responses were assessed at baseline and after the first and second dose by hemagglutination inhibition (HAI) and microneutralization (MN) assays, with 72% of the high-dose and 68% of the low-dose vaccine recipients presenting a ⩾4-fold response in the HAI assay and 72% of the high-dose and 61% of the low-dose vaccine recipients exhibiting a ⩾4-fold response in the MN assay. These promising results support further development. ClinicalTrials.gov number NCT02171819, June 20, 2014.

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## 1. Introduction

The 2009 influenza A/H1N1 pandemic illustrates the unpredictability of the influenza virus and supports a call for significant preparedness efforts across the globe to anticipate new threats. The effects of an influenza pandemic are likely to be greatest in resource-limited countries where individuals may be more susceptible to severe outcomes of influenza due to underlying nutritional deficiencies and concomitant illness, poorer sanitary conditions, limited access to health care, and the lack of widespread use of vaccines for influenza as well as against common causes of bacterial pneumonia [1]. During the influenza A/H1N1 pandemic, vaccine availability was limited in industrialized countries and was significantly delayed in low-resource countries.

Since 1996, highly pathogenic influenza A/H5N1 avian viruses have caused widespread outbreaks in poultry with high mortality as well as sporadic, severe, and fatal disease in humans [2]. From 2003 through 2016, the World Health Organization (WHO) confirmed 850 human cases of influenza A/H5N1 influenza infection, with 449 deaths [3]. Southeast Asian countries, including Vietnam, have been disproportionately affected by influenza A/H5N1 accounting for 48.2% of all confirmed influenza A/H5N1 cases reported during that period. Influenza A/H5N1 infection in animals is now thought to be endemic in the region [4]. By May 2016, Vietnam had reported 125 confirmed human cases, with 62 deaths [5].

Influenza vaccination is considered the optimal approach to prevent infection and/or limit severe illness. Vaccination could target individuals that may be exposed to zoonotic transmission, or to

☆ This study was approved by the Ethics Committee in Medical Biological Research at the Pasteur Institute, Ho Chi Minh City, Vietnam; Research Ethics Review Committee, World Health Organization (WHO), Geneva, Switzerland; and Ethics Committee in Biomedical Research of the Ministry of Health (MOH), Hanoi, Vietnam. PATH's Research Ethics Committee formally delegated review of this study to the WHO Ethics Committee.

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the general population or segments of it, depending on vaccine availability, in the event of a pandemic threat. If an influenza A/H5N1 pandemic were to occur, the vaccine demand to control it would be enormous. There is a substantial need for local development, production, and stockpiling of influenza A/H5N1 and other pandemic influenza vaccines (such as A/H7N9) in Vietnam for pandemic preparedness. To date, however, no influenza A/H5N1 vaccine has been licensed in Vietnam. To address this, the Vietnam Institute of Vaccines and Medical Biologicals (IVAC) has manufactured pandemic influenza vaccine candidates, including influenza A/H1N1, A/H5N1, and A/H7N9, as well as a trivalent seasonal vaccine candidate under guidance from the Vietnam Ministry of Health (MOH). IVAC has tested the A/H1N1 vaccine candidate in clinical trials [6]. We present in this manuscript the results of testing IVAC's influenza A/H5N1 vaccine candidate in a Phase 1 clinical trial to initiate the assessment of its safety and immunogenicity.

## 2. Methods

### 2.1. Study design and implementation

Clinical testing of the influenza A/H5N1 vaccine candidate was conducted as a Phase 1, double blinded, randomized, placebo-controlled study at a community clinic in the Ben Luc District, Long An Province, Vietnam. The primary objective of the study was to evaluate the safety profile of two intramuscular doses of the vaccine, the secondary objective was to evaluate its immunogenicity. Seventy-five healthy male and female adults, 18–30 years of age, were enrolled into the trial to receive two doses of vaccine or placebo three weeks apart. Subjects were randomized to one of the following three treatment allocations: 32 subjects to 7.5 mcg/dose vaccine (low-dose), 31 subjects to 15 mcg/dose vaccine (high-dose), and 12 subjects to placebo. This sample size was selected to enable at least 30 evaluable subjects in each of the groups to receive active vaccine. The study was double blinded to study subjects, investigators, and the sponsor until the clinical and laboratory data were completed, fully reviewed, and the database was locked.

In order to be included in the study, subjects had to be healthy (from medical history and physical exam), aged 18–30 years; willing to provide written informed consent; capable and willing to complete diary cards; and willing to return for all visits. Females were asked to utilize reliable birth control measures. Exclusion criteria included: participation in another clinical trial involving receipt of any non-study vaccine or immunoglobulins within four weeks of enrollment; current or recent acute illness with or without fever; chronic administration of immunosuppressants; history of asthma; or hypersensitivity after previous administration of any vaccine, to any of the vaccine components, including chicken or egg protein, food, or environmental allergens. Injections of study product were staggered to allow for an initial safety evaluation of a sentinel cohort of 19 subjects, which preceded the remainder of the study group by approximately two to three weeks. Once all of the volunteers in the sentinel group received a dose of study vaccine and safety information for seven days post-vaccination was available, the data were reviewed by a safety monitoring committee composed of independent experts not associated with the study, who provided a recommendation to vaccinate the rest of the study cohort.

### 2.2. Rationale for study design

After consultation with a Product Development Advisory Group that includes members from WHO, IVAC, PATH, the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA), and independent consultants expert in influenza vaccine development, IVAC chose to evaluate two dose levels of vaccine, 7.5 and 15 mcg hemagglutinin (HA) content per 0.5 mL dose given 21 days apart. The doses were chosen because pandemic monovalent vaccines for influenza A/H5N1 strains are known to require a higher HA content than what was used for influenza A/H1N1 vaccines during the recent pandemic or used for other human influenza strains, and at the same time to identify an effective dose lower than the high-doses used with other H5N1 products (doses of 30–45 mcg have been used by Sanofi, Microgen, or CSL).

### 2.3. Investigational product

The study product was inactivated, whole virion, monovalent influenza A/H5N1 vaccine candidate (IVAC/Nha Trang). The vaccine was produced in embryonated eggs, inactivated with formalin, and formulated with aluminum hydroxide 0.6 mg/0.5 mL. The following two different doses of vaccine were tested: 7.5 mcg (low-dose) and 15 mcg (high-dose) per 0.5 mL. IVACFLU-A/H5N1 was filled in single dose vials. Each 0.5 mL dose may have contained residual amounts of formaldehyde (not more than 0.02%) and sucrose (not more than 2.0%). Placebo consisting of phosphate buffered saline (PBS) was also manufactured by IVAC. A 0.5 mL single-dose vial with a pH of 7.2 was used per injection.

Two lots of IVACFLU-A/H5N1 vaccine and one lot of placebo were used in the study. They were examined for quality control by the National Institute of Control Vaccine and Medical Biologicals and were granted the certificate of quality that met the requirements on physical properties, pH, aluminum concentration, protein concentration, potency, identity, general safety, endotoxin, and sterility.

Study vaccine and placebo were labeled at IVAC in compliance with MOH's drug labeling regulations before they were shipped to Pasteur Institute-Ho Chi Minh City (PI-HCMC) for storage and to the study site at the Ben Luc District Health Center for use. To blind the vaccinator and study subjects, a nurse with no other study duties was responsible for withdrawing study product from vials according to the randomization schedule. The aluminum hydroxide adjuvant in the vaccine gave it a slightly different appearance from the placebo, therefore, in order to maintain the blinding, the nurse masked the syringe before handing it over to the vaccinator by covering the original label with an identical study label containing only the study product code of each subject.

### 2.4. Assigning subjects to study groups

Each subject was assigned a unique screening number after signing the screening informed consent. Once the subject was considered to be eligible and he or she signed the consent for the vaccine portion of the study, the subject was randomized by assigning a unique subject identification number sequentially in ascending order from the randomization schedule. The mechanics of the randomization was the responsibility of a PATH staff scientist not otherwise involved with the trial. A permuted block randomization method with the block size of 19 was used to computer generate a randomization schedule with a pre-specified ratio of 8:8:3 (low-dose vaccine: high-dose vaccine: placebo). The randomization schedule was produced using SAS computer software and consisted of the subject identification number and the corresponding treatment assignment. The first 19 subjects enrolled were treated as a "sentinel" cohort before the remaining 57 subjects were enrolled. For both, the sentinel cohort and the rest of the cohort the pre-specified randomization ratio of 8:8:3 was used.

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