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Immunological priming induced by a two-dose series of H5N1 influenza antigen, administered alone or in combination with two different formulations of AS03 adjuvant in adults: Results of a randomised single heterologous booster dose study at 15 months

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ABSTRACT

One influenza pandemic preparedness strategy involves priming a population with a pre-pandemic subtype-specific vaccine and boosting the immunological response at the time of the pandemic with a strain-matched vaccine. In the current study, adults (n = 469) randomised 15 months previously to receive an A/Indonesia/5/2005 (H5N1) influenza vaccine (3.75 μg haemagglutinin antigen [HA]) administered alone or in combination with an oil-in-water emulsion based Adjuvant System containing 11.86 mg ($AS03_A$) or 5.93 mg ($AS03_B$) tocopherol per dose, received one booster dose of A/turkey/Turkey/1/2005 (H5N1) vaccine (3.75 μg HA) with or without $AS03_A$. An anamnestic antibody response that met US regulatory acceptance criteria was observed 15 months after priming. Although superior immunogenicity of AS03-adjuvanted compared to unadjuvanted priming was not demonstrated, higher antibody titres which persisted longer were seen when both priming and boosting regimens were adjuvanted. This may affect duration of response or heterologous immunity. The booster vaccines had a clinically acceptable safety/reactogenicity profile after adjuvanted or unadjuvanted priming. This study has been registered at www.clinicaltrials.gov NCT00771615.

1. Introduction

Influenza pandemics occur when a novel influenza virus emerges against which the great majority of the world's population lacks immunity. The precise timing and impact of influenza pandemics remain unpredictable [1], but virological surveillance in both humans and potential reservoir species such as birds and swine may provide some advance warning. Since 1997, hundreds of cases of influenza in humans following infection with avian influenza viruses of different subtypes have been reported, with H5N1 strains being the most common [2,3]. H5N1 infection has been associated with high mortality rates and pre-existing immunity is essentially absent in the general population [3,4]. H5N1 viruses are divided into different clades on the basis of their haemagglutinin sequences and the majority of recent isolates associated with human disease belong to clade 1 or clade 2 [5–7]. While human-to-human transmission is extremely rare, the potential for a pandemic outbreak exists if these viruses acquire, by reassortment or mutation, the ability to pass efficiently from human to human and cause disease [1,8]. H5N1 viruses that cause human infections are seen by the World Health Organization (WHO) as a potential pandemic threat, and development of pre-pandemic vaccines against these strains is therefore needed [9].

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; AS03, oil-in-water emulsion based Adjuvant System containing tocopherol; ATP, according to protocol; CBER, Center for Biologics Evaluation and Research; CI, confidence interval; FDA, Food and Drug Administration; GMT, geometric mean titres; GSK, GlaxoSmithKline; HA, haemagglutinin antigen; HI, haemagglutination inhibition; LL, lower limit; MedDRA, Medical Dictionary for Regulatory Activities; MN, microneutralisation; pIMD, potential immunologically mediated disease; SAE, serious adverse event; SCR, seroconversion rate; SPR, seroprotection rate; TVC, total vaccinated cohort; VRR, vaccine response rate; WHO, World Health Organization.

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Vaccination is considered to be the most effective strategy for the mitigation of morbidity and mortality caused by influenza pandemics [10,11]. However, as occurred during the influenza A H1N1 pandemic in 2009, production of a vaccine that matches a pandemic influenza strain can take four to six months from the time a pandemic virus is identified by the WHO [9,12]. Production capacity is another constraint, especially if two vaccine doses are needed or if the same manufacturing facilities must also support seasonal vaccine production [4,8,10]. Worldwide spread of infection is therefore possible before a sufficient amount of vaccine could be manufactured and delivered to vulnerable populations. To overcome these limitations, a strategy of priming at-risk populations with a pre-pandemic vaccine, containing antigens derived from a prototype strain of a pandemic threat subtype, has been proposed to improve the speed and enhance the amplitude of the response to a subsequent booster regimen matching the actual pandemic strain [9,12]. Pre-pandemic vaccines need to display broad cross-reactive immunogenicity against non-vaccine H5N1 strains since it is not possible to predict the evolution of the H5N1 viruses or which strain will become pandemic [6–8,13]. In order to meet global demand, vaccines containing low doses of influenza antigen are preferable. One potential strategy for achieving both objectives is the use of oil-in-water emulsion based Adjuvant System to significantly improve the immunogenicity of pandemic vaccines, thereby allowing the quantity of antigen to be limited while eliciting a broadly cross-reactive response [4,8,11,13–16].

An influenza A/Vietnam/1194/2004 (H5N1) (clade 1) pre-pandemic vaccine (*Prepandrix*™, GlaxoSmithKline [GSK] Biologicals) combined with an oil-in-water emulsion based Adjuvant System containing tocopherol (AS03) has been approved in the European Union for use in adults aged 18–60 years [17,18]. Two doses of this AS03-adjuvanted vaccine, given at a 21-day interval, produce antibody levels against the vaccine-homologous virus that meet US regulatory criteria, as well as substantial levels of cross-reactive antibodies against viruses of other H5N1 clades [4,6,8,13]. Presently, vaccines against more recent H5N1 drift variant strains, such as A/Indonesia/5/2005 (clade 2.1) and A/turkey/Turkey/1/2005 (clade 2.2), have been developed [7,19].

This study was designed to investigate whether two priming doses of AS03-adjuvanted A/Indonesia/5/2005 (H5N1) vaccine followed by boosting with a single dose of AS03-adjuvanted A/turkey/Turkey/1/2005 (H5N1) vaccine at an interval exceeding one year is a viable pandemic preparedness strategy, and to determine the safety and immunogenicity of AS03 adjuvantation in the priming and booster vaccine regimens.

2. Materials and methods

2.1. Study design

This study is a follow-up of a randomised controlled trial of healthy adults who were allocated to a two-dose schedule of adjuvanted or unadjuvanted H5N1 influenza vaccines (NCT0051087; for more details, we refer to the study performed by Langley and colleagues) [19]. In this follow-up study (15 months after the primary study), participants received a single dose of a drift variant H5N1 vaccine in which the antigen differed from the primary series. The primary study was performed between July 2007 and July 2008 in seven centres in the United States (US) and three centres in Canada, and the follow-up study between October 2008 and December 2009 in the same study population (Fig. 1).

In the primary study, healthy subjects aged 18–64 years received two doses of A/Indonesia/5/2005 (H5N1) vaccine (3.75 μg haemagglutinin antigen [HA]) administered either without adjuvant, with $AS03_A$ adjuvant (containing 11.86 mg tocopherol per dose) or with $AS03_B$ adjuvant (containing 5.93 mg tocopherol per dose). In this follow-up study, the subjects received a single booster dose of A/turkey/Turkey/1/2005 (H5N1) (3.75 μg HA) vaccine administered either with or without $AS03_A$ adjuvant about 15 months after the administration of the first dose in the primary vaccination series. Subjects primed with $AS03_A$-adjuvanted and $AS03_B$-adjuvanted vaccines were randomised (3:2) to receive an $AS03_A$-adjuvanted booster dose ($AS03_A$/$AS03_A$ and $AS03_B$/$AS03_A$ groups) or an unadjuvanted booster dose ($AS03_A$/unadjuvanted and $AS03_B$/unadjuvanted groups). All subjects primed with the unadjuvanted vaccine (of whom a smaller number was available based on the design of the primary study) received an $AS03_A$-adjuvanted booster dose (unadjuvanted/$AS03_A$ group). The five parallel groups thus created are seen in Figs. 1 and 2.

Treatment allocation was performed using a central randomisation system on the Internet. The randomisation algorithm considered the primary treatment regimen and used a minimisation procedure accounting for centre and age (18–40 years old versus 41–64 years old at the time of the first priming dose administration). Centre and age minimisation factors had equal weight in the minimisation algorithm. Vaccines were prepared and administered by authorised medical personnel who had no further involvement in the trial or with the study subjects. Subsequent assessments were performed by blinded observers who were unaware of which vaccine was administered to the subject.

All subjects attended formal study centre visits for safety and immunogenicity assessments prior to vaccination (Day 0) and on Day 10, Day 42 and Day 182 following the booster dose. A safety visit was conducted via telephone call on Day 84 and Day 364 (Fig. 1).

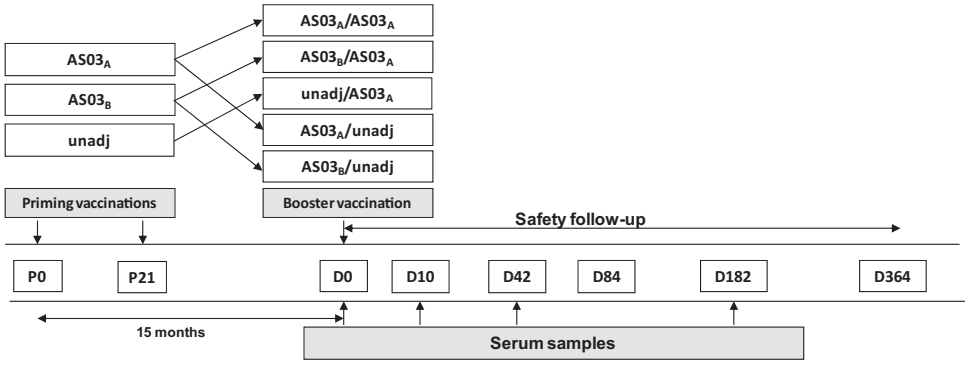

Fig. 1. Study design. P0 = time of the first priming dose administration; P21 = P0 + 21 days = time of the second priming dose administration; D0 = P0 + average 15 months = time of the booster dose administration; D10, D42, D84, D182 and D364, respectively, 10, 42, 84, 182 and 364 days after the booster dose administration; Priming vaccination = vaccination with A/Indonesia/5/2005 (H5N1) vaccine; Booster vaccination = vaccination with A/turkey/Turkey/1/2005 (H5N1) vaccine.