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Extrapolating theoretical efficacy of inactivated influenza A/H5N1 virus vaccine from human immunogenicity studies

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ABSTRACT

Influenza A virus subtype H5N1 has been a public health concern for almost 20 years due to its potential ability to become transmissible among humans. Phase I and II clinical trials have assessed safety, reactogenicity and immunogenicity of inactivated influenza A/H5N1 virus vaccines. A shortage of vaccine is likely to occur during the first months of a pandemic. Hence, determining whether to give one dose to more people or two doses to fewer people to best protect the population is essential. We use hemagglutination–inhibition antibody titers as an immune correlate for avian influenza vaccines. Using an established relationship to obtain a theoretical vaccine efficacy from immunogenicity data from thirteen arms of six phase I and phase II clinical trials of inactivated influenza A/H5N1 virus vaccines, we assessed: (1) the proportion of theoretical vaccine efficacy achieved after a single dose (defined as primary response level), and (2) whether theoretical efficacy increases after a second dose, with and without adjuvant. Participants receiving vaccine with AS03 adjuvant had higher primary response levels (range: 0.48–0.57) compared to participants receiving vaccine with MF59 adjuvant (range: 0.32–0.47), with no observed trends in primary response levels by antigen dosage. After the first and second doses, vaccine with AS03 at dosage levels 3.75, 7.5 and 15 mcg had the highest estimated theoretical vaccine efficacy: Dose (1) 45% (95% CI: 36–57%), 53% (95% CI: 42–63%) and 55% (95% CI: 44–64%), respectively and Dose (2) 93% (95% CI: 89–96%), 97% (95% CI: 95–98%) and 97% (95% CI: 96–100%), respectively. On average, the estimated theoretical vaccine efficacy of lower dose adjuvanted vaccines (AS03 and MF59) was 17% higher than that of higher dose unadjuvanted vaccines, suggesting that including an adjuvant is dose-sparing. These data indicate adjuvanted inactivated influenza A/H5N1 virus vaccine produces high theoretical efficacy after two doses to protect individuals against a potential avian influenza pandemic.

1. Background

Influenza A virus subtype H5N1, an avian influenza strain, has been a serious public health concern for almost 20 years because of its virulence and potential to become transmissible among humans [1]. From 2003 to September 17, 2015, 844 confirmed human cases of H5N1 infection with 449 deaths occurred in 16 countries [2]. Because of the high case fatality ratio (53%) and negligible population immunity, a deadly pandemic could result if the virus becomes readily transmissible between persons [3,4]. If a pandemic were to start, a pandemic strain-specific vaccine would need to be produced and deployed rapidly [5]. Vaccines stockpiled

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for immediate deployment may not match the pandemic virus, however the stockpiled H5N1 influenza vaccines may provide some heterologous protection to similar clades [6–8], suggesting stockpiled vaccine could be a first-line intervention while well-matched vaccine is produced.

To prepare for a possible A/H5N1 pandemic, phase I and II clinical trials have assessed the safety, reactogenicity and immunogenicity of inactivated influenza A/H5N1 virus vaccines. However, the efficacy of H5N1 vaccines in humans remains unproven [9]. Animal challenge studies suggest these vaccines are protective [10–12], but extrapolating these results to efficacy in humans remains poorly understood. Generally two doses of vaccine are recommended to achieve full efficacy for an individual. However, at the population level, depending on the efficacy achieved with one dose, vaccinating a larger proportion of the population with a single dose could achieve a greater reduction in morbidity and transmission [13]. Currently, there are no estimates of vaccine efficacy for either one or two doses of avian influenza vaccines. Given the limited vaccine supply and time constraints during a pandemic, determining the efficacy is essential for optimal allocation of resources.

The aim of this study is to close this gap by providing theoretical efficacy estimates for avian influenza vaccines. Hemagglutination–inhibition (HAI) antibody titer is widely recognized as a correlate of protection against seasonal influenza infection. Currently, this is the only correlate of protection used for licensure in the US [14], although secretory IgA and anti-neuraminidase antibodies have also been shown to correlate with protection [15,16]. Based on Hobson et al. [17] it is believed an HAI antibody titer of 40 is associated with 50% protection against seasonal influenza illness in healthy adults. However, little is known about the relationship between HAI antibody titer and protection against specific viral strains (or influenza A/H5N1 viruses), and the influence of host factors such as age [18]. In Coudeville et al. [19], data from 15 seasonal influenza vaccine studies (six challenge studies, five clinical trials and four cohort studies) reported between 1945 and 2006, were used to construct a continuous curve estimating level of protection at varying levels of HAI titers against illness caused by seasonal influenza strains. Fourteen of the studies included adults aged 18–60, and one included adults aged 60 years or greater. The protection measured was against a mixture of infection and illness. For the purpose of this analysis, we assume that avian influenza vaccine-induced protection is similar to that of seasonal influenza vaccines, and the HAI protection curve of Coudeville et al. provides a theoretical estimate of inactivated influenza A/H5N1 vaccine efficacy against avian influenza infection or illness. Under these assumptions, we analyzed data from 14 phase I and phase II clinical trials to estimate the proportion of theoretical efficacy achieved after the first and second doses of vaccine, and to assess the impact of antigen dosage and adjuvant on vaccine efficacy.

2. Methods

Data from 14 phase I and eight phase II randomized clinical trials assessing safety, reactogenicity and immunogenicity of inactivated influenza A/H5N1 virus vaccines were made available by the National Institute of Allergy and Infectious Diseases (NIAID), NIH. Healthy people between the ages of 18 and 99 years volunteered to participate in these trials. Within each trial, eligible subjects were randomized to receive two doses of varying dosages of vaccine antigen with or without one of two adjuvants: MF59 or Adjuvant System 03 (AS03). Some studies included a placebo arm. MF59 and AS03 adjuvants are both oil-in-water emulsions manufactured by Novartis Vaccines and GlaxoSmithKline (GSK), respectively. Only vaccine trial arms including A/H5N1 virus vaccine-naïve participants who received two intramuscular doses of 3.75, 7.5, 15, or 90 mcg of vaccine spaced 14–180 days apart were considered for inclusion in the analysis.

We included only trial arms with vaccines that had estimated theoretical efficacies greater than 60% after two doses, which corresponds to the curve given by Coudeville et al. to geometric mean HAI titers (GMT) > 24. This decision was based on findings that recent influenza epidemics have had basic reproductive numbers (the expected number of secondary infections resulting from a typical infectious person in a completely susceptible population [20]), in the range of approximately 1.6–1.8 [21,22]. Assuming vaccine coverage in a targeted vaccination group during a future epidemic will be 70% at best, the estimated lower bound of vaccine efficacy to control the epidemic will be about 60% [23]. For example, if the basic reproductive number during an epidemic is 1.7, and vaccine coverage is 70%, vaccine efficacy would need to be at least 59% to control transmission in a homogeneously mixing population [24].

We did not exclude any data based on antigen manufacturer, type of adjuvant used, or the population of the study. Thirteen trial arms from six trials exhibited estimated theoretical efficacies greater than 60% and were therefore included in this analysis (Table 1). Seven of the trial arms used vaccines with either MF59 or AS03 [25–27]. The remaining six trial arms used an antigen dosage of 90 mcg and no adjuvant [6,28]. One of those six trial arms used 45 mcg of one clade (H5 A/Indo) and 45 mcg of another clade (H5 A/Vietnam) at each dose. All but one of the thirteen trials arms (the Chiron antigen was used in trial #04-062) used a Sanofi antigen.

Using a per protocol analysis, GMT and 95% confidence intervals were calculated for each trial arm 14–28 days after the first dose of vaccine was administered and again for each arm, 21–28 days after administration of the second dose. By extracting data points from the HAI protection curve (Fig. 1) in Coudeville et al., theoretical vaccine efficacy and 95% credible intervals, the Bayesian analog of confidence intervals, were estimated from the GMT for each trial arm after one and two doses. We employed these same methods to conduct a sensitivity analysis using the HAI protection curve presented in Tsang et al. [29].

We define the primary response level as the proportion of the overall maximum efficacy obtained after a single dose of vaccine. For example, if a vaccine had an overall efficacy of 80% after two doses, a primary response level of 50% corresponds to obtaining half of the protection after one dose (40% vaccine efficacy after one dose). Primary response levels are useful measures because they allow us to parameterize mathematical and computer models that will compare vaccination strategies with multiple doses of vaccine [13]. We calculated the primary response level for each combination of vaccine, dosage and adjuvant using the ratio of the estimated theoretical vaccine efficacy after the first dose over the estimated theoretical vaccine efficacy after the second dose.

Using STATA 12, an unadjusted weighted linear regression was used to determine whether there was a significant absolute difference in GMT between adjuvanted vaccines (AS03 and MF59) and unadjuvanted vaccines, and to determine whether there was a significant absolute difference in GMT by antigen dosage (3.75, 7.5, 15, and 90 mcg). For the regression analysis, the weights chosen were based on the sample size of each arm and were inversely proportional to the variance of each GMT included in the regression model. Unpaired *t*-tests with unequal variances were used to determine mean GMT, mean estimated theoretical vaccine efficacy and mean primary response level by whether vaccines had adjuvants or not.

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