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Review

A systematic review and meta-analysis of cross-reactivity of antibodies induced by oil-in-water emulsion adjuvanted influenza H5N1 virus monovalent vaccines

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ABSTRACT

Background: Cross-clade immunogenic stockpiled H5N1 vaccines may decrease the morbidity and transmission of infection during the initial phase of influenza pandemic. Meta-analysis of cross-reactive antibodies induced by oil-in-water emulsion adjuvanted (OWEA) influenza H5N1 virus monovalent vaccines with circulating heterologous H5N1 virus strains, isolated from human infections was performed.

Methods: Literature search of MEDLINE, EMBASE, Web of Knowledge, The Cochrane Library, ClinicalTrials.gov, and International Standard Randomised Controlled Trial Number registry was conducted up through December 1, 2015. Methodologically qualified studies were included for (1) use of two doses of licensed OWEA (AS03 or MF59) egg-derived, inactivated influenza H5N1 virus monovalent vaccine, (2) participant age between 18 and 64 years, and (3) evaluation of immunogenicity outcome for one or more subclade. Meta-analysis assessed the cross-reactivity of antibodies elicited by clade 1 adjuvanted vaccine strain against clade 2.1 virus strain (A/Vietnam/1194/2004 vs. A/Indonesia/05/2005); and separately against clade 2.2 virus strain (A/Vietnam/1194/2004 vs. A/turkey/Turkey/1/05); and clade 2.1 adjuvanted vaccine strain against clade 1 virus strain (A/Indonesia/05/2005 vs. A/Vietnam/1194/2004). Quantitative publication bias and influence analysis was conducted to evaluate potential impact of unpublished or new studies on the robustness of meta-analysis.

Results: Of 960 articles, 53 qualified for quality assessment and 15 studies met the inclusion criteria. All assessed clade pairs elicited cross-reactive antibodies (clade 1 against clade 2.1 and 2.2; clade 2.1 against clade 1, 2.2, and 2.3). Heterologous strains of same sub-clade are likely to elicit higher cross-reactive antibodies.

Conclusions: OWEA influenza H5N1 virus monovalent vaccines exhibit broad cross-clade immunogenicity, a desired feature for vaccine stockpiling not yet demonstrated by unadjuvanted vaccines. In case of an impending H5N1 virus pandemic, stockpiled OWEA influenza H5N1 virus monovalent vaccines may allow population priming that could slow down the course of pandemic and could offer additional time needed for development of an effective strain specific vaccine supply.

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1. Introduction

The highly pathogenic avian influenza H5N1 virus poses a potential public health threat to cause a human pandemic. From 2003 to 2015, 53% of WHO confirmed human A/H5N1 influenza infection cases have resulted in deaths [1,2]. Emergence of H5N1 virus with the capacity for human-to-human transmission while maintaining high pathogenicity may result in a pandemic with high mortality rates [1,2]. Also, reports on possible aerosol or respiratory droplet transmission of H5N1 virus among mammals have increased concerns about a future pandemic [3,4]. As of 2015, clade 1 (1.1), clade 2 (2.1.3.1, 2.2.1, 2.3.2.1, 2.3.4.2) and clade 7 (7.2) H5N1 viruses have been reported to circulate in poultry and humans [1,2,5]. The continuous spread, rapid evolution, and diversification of the H5N1 viruses have highlighted the need for advance stockpiling of H5N1 vaccines [6–10].

Vaccine efficacy depends on the strength of the match between the vaccine and circulating virus strains; the production and delivery of a strain-matched pandemic vaccine may require four to six months [2,11–13]. The pre-requisites of an optimal stockpiled pandemic vaccine are: (1) safety and immunogenicity, (2) antigen dose sparing (i.e., to result in effective immunization at low antigen doses), (3) broad cross-reactivity against phylogenetically and antigenically distinct variant virus clades and (4) induce long-lived immunological memory [12–19]. Cross-reactivity is defined as the ability of an antibody elicited by the administered vaccine to react with other circulating and emerging drift variants of the vaccine strain [20]. Vaccination of naïve humans with a cross-clade immunogenic stockpiled H5N1 vaccine may offer some (limited) degree of protection and thereby, decrease the morbidity and transmission of infection during the initial phase of the pandemic until the matched strain vaccines become available.

Several inactivated influenza H5N1 virus monovalent vaccines have been licensed by worldwide regulatory agencies for use in the initial phase of a pandemic [1,5,19]. Two egg-derived, inactivated oil-in-water emulsion adjuvanted (OWEA) influenza H5N1 vaccines have received marketing authorization from the Committee for Medicinal Products for Human Use (CHMP) in Europe [6,7,16]. These approved vaccines contain either GlaxoSmithKline Biologicals' proprietary AS03 adjuvant or Novartis Vaccines and Diagnostics' proprietary MF59 [1,10]. One such adjuvanted vaccine containing AS03 adjuvant was licensed by the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration [13–15]. Two doses of egg-derived inactivated, OWEA influenza H5N1 virus monovalent vaccines have shown antigen dose-sparing in humans [8,9,17,18,21–25] and induction of antibodies that are cross-reactive against heterologous strain [1,10,25,26]. These adjuvanted vaccines also demonstrated improved quality of antibody responses in terms of epitope breadth and increased binding affinity to the hemagglutinin globular head that contains most of the protective epitopes [17,18].

The objectives of this study are to: (1) conduct a systematic review of articles that assessed the cross-reactivity induced by AS03 or MF59 adjuvanted influenza H5N1 virus monovalent vaccines, and (2) use data from published studies to perform a meta-analysis of cross-reactive antibodies generated by OWEA influenza H5N1 vaccine strains (clade 1, clade 2) against circulating strains (clade 2, clade 1, clade 2.2, clade 2.3).

2. Methods

Data Sources: A core literature search of the COSI (COre-Standard-Ideal) model was applied to maximize the yield of published and indexed literature from sources relevant to the systematic review [27]. MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com), Web of Knowledge (http://apps.webofknowledge.com), The Cochrane Library (http://www.cochranelibrary.com), ClinicalTrials.gov (http://clinicaltrials.gov), and International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.controlled-trials.com/isrctn) were selected as the relevant data sources. A search was conducted up through December 1, 2015 without language restrictions. The search terms were "adjuvanted H5N1 influenza vaccine", "oil in water adjuvanted H5N1 vaccine", and "cross-reactivity of adjuvanted H5N1 vaccine". Also, to achieve maximum sensitivity, the terms "AS03" and "MF59" were appended to the above search terms.

Study Selection: The primary study selection criteria (Fig. 1) was based on exclusion of non-original articles, conference and congress abstracts, technology briefings, meeting reports, editorials, comments, letters, non-systematic review articles, non-English based articles, preclinical trials in experimental animal models, human clinical trials and articles related to non-H5N1 avian influenza (H1N1, H7N9) or seasonal influenza, unadjuvanted H5N1 vaccines, or adjuvants other than AS03 or MF59. After primary screening to exclude non-relevant articles, publications were retrieved for detailed assessment.

Two FDA reviewers (KC, ML) assessed the quality of reported studies. Each selected article was assessed using the Jadad scale [28] for the methodological quality based on randomization, blinding of the study, and information on participant dropouts or withdrawals. Each article could be allotted a maximum score of 5. One point was allotted if the study mentioned the randomization method and an additional point was allotted for an appropriate method of randomization. One point was allotted for describing the blinding method and an additional point was allotted for an appropriate method. One point was allotted for description of fate of all participants in the study. Articles with a Jadad score ≥ 3 were selected. All the Jadad qualifying articles were screened for additional exclusion criteria related to data reporting for immunogenic endpoints (Fig. S1).

Inclusion criteria (Fig. 1) were: (1) use of two doses of OWEA egg-derived, inactivated influenza H5N1 virus monovalent vaccine (3.75 μg HA for AS03 adjuvanted vaccine or 7.5 μg HA for MF59 adjuvanted vaccine), (2) participant age between 18 and 64 years, and (3) evaluation of immunogenicity outcome for one or more subclade.

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