Immunogenicity and adverse events of avian influenza A H5N1 vaccine in healthy adults: multiple-treatments meta-analysis


CRD summary
H5N1 vaccine formulations including a low haemagglutinin antigen dose and a non-aluminium adjuvant might be the best available option in the event of a avian H5N1 influenza pandemic. The review was well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the ability to evoke an immune response (immunogenicity) and adverse event profile of avian influenza A H5N1 vaccines.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, the World Health Organization clinical trial registry, and ISRCTN register were searched, without language restrictions, to February 2009. Search terms were reported and the reference lists of all retrieved articles and reviews were checked for further studies.

Study selection
Randomised controlled trials (RCTs) that assessed H5N1 immunogenicity and side effects in healthy humans, who had not previously received H5 vaccines, were eligible for inclusion. Trials that evaluated only one vaccine formulation were excluded.

The included trials took place in the United States, Australia, Europe, and Asia. The participants were aged between 18 and 65 years and received doses of vaccine varying from 1.25μg to 30μg of haemagglutinin antigen, with and without aluminium or other treatment. All the vaccine formulations were inactivated and classified as either sub-virion or whole viruses. The primary outcome was the immunogenicity of the vaccine defined as the seroconversion or seroresponse measured by haemagglutination inhibition or micro-neutralisation. Satisfactory immunogenicity was defined before selection by the reviewers as 70%. Secondary outcomes included adverse events assessed between seven and 10 days, such as fever, headache, myalgia or muscle pain, malaise or fatigue, and local reactions, such as injection-site pain and erythema or redness.

The authors did not state how the trials were selected for review.

Assessment of study quality
The methodological quality of the trials was assessed using the Jadad scale. They were assessed on randomisation, blinding, and dropouts or withdrawals.

Two independent reviewers assessed trial quality.

Data extraction
Data were extracted to permit the calculation of odds ratios (ORs) and risk differences (RDs) with 95% credible intervals (CIs). If trials reported data on both seroconversion and seroresponse, data were extracted only for seroconversion.

The authors did not state how many reviewers performed the data extraction. [A: Two independent reviewers extracted the data. Any disagreements were resolved by arbitration with two further reviewers.]
Methods of synthesis
A Bayesian framework was used to conduct a multiple treatments meta-analysis, combining data from direct and indirect comparisons across all possible regimens (including placebo). Posterior ORs were translated to RDs against the baseline dosing regimen of 6μg of haemagglutinin antigen or less without additional treatment. The results were pooled separately for seroconversion or seroresponse measured by haemagglutination inhibition and for seroconversion or seroresponse measured by micro-neutralisation.

For the secondary analyses, the results were grouped according to outcome and pooled risk ratios (RRs) with 95% CIs were calculated using random-effects models for direct comparisons. Data on adverse events were only pooled for direct comparisons as these data were considered inappropriate for the meta-analysis. The Mantel-Haenszel fixed-effect model was used to check agreement with the conclusions derived from the random-effects models. Statistical heterogeneity was evaluated using the I^2 test.

Results of the review
Twelve articles of thirteen trials, with 9,723 patients, were included. These analysed 58 treatment groups, of which 52 reported data on haemagglutination inhibition and 57 reported data on micro-neutralisation. The Jadad scores in 11 trials were between three and five out of five, indicating fair-to-good quality. One trial scored one on the Jadad scale and one was assigned a Jadad score of two.

Compared with a baseline dose of 6μg or less of non-enhanced vaccine, the meta-analysis found that immunogenicity increased with the use of non-aluminium-enhanced vaccines, using haemagglutination inhibition, from 6μg or less (OR 78.06, 95% CI 13.2 to 574) to 30μg or more of haemagglutinin antigen (OR 93.70, 95% CI 16.0 to 692). Using micro-neutralisation, it also increased from 6μg or less (OR 16.19, 95% CI 3.94 to 66.8) to 30μg or more of haemagglutinin antigen (OR 28.05, 95% CI 6.63 to 129).

Immunogenicity increased with increasing haemagglutinin antigen dose, but 70% was not attained with aluminium-enhanced or non-enhanced formulations at any dose.

There were no serious adverse events reported in any of the trials. There were significantly higher risks of myalgia with enhanced vaccines compared with non-enhanced formulations at a dose of 15μg of haemagglutinin antigen (RR 2.44, 95% CI 1.80 to 3.31). The non-aluminium-enhanced vaccines were found to have significantly higher risks of headache (RR 1.57, 95% CI 1.04 to 2.36), malaise (RR 1.54, 95% CI 1.04 to 2.28), myalgia (RR 3.50, 95% CI 1.74 to 7.01), and local pain (RR 2.37, 95% CI 1.73 to 3.25), but not fever and erythema. There was no evidence to suggest that higher doses of haemagglutinin antigen increased the risk of adverse events, except for local pain with higher risks observed with 30μg compared with the 15μg dose (RR 1.40, 95% CI 1.14 to 1.71).

Authors’ conclusions
H5N1 vaccine formulations including a low haemagglutinin antigen dose and a non-aluminium adjuvant might represent the best available option in the event of an avian H5N1 influenza pandemic. The evidence suggested that the vaccine formulations were well tolerated at any dose and the adverse events observed could be regarded as clinically acceptable. Further research was required to verify the high immunogenicity of non-aluminium-enhanced vaccine formulations that used small quantities of haemagglutinin antigen.

CRD commentary
This review addressed two clearly stipulated questions. The search was comprehensive, with no language bias and attempts were made to search for unpublished trials. Steps taken to minimise errors and bias were reported for the assessment of methodological quality, but it was unclear whether such steps were taken for trial selection and data extraction. The quality of most of the included trials was judged to be high by their summary scores, but the authors did not consider the methodological quality in their analysis of the results. The methods used to conduct the meta-analyses were appropriate.

The review was well conducted and the authors’ conclusions are likely to be reliable.
Implications of the review for practice and research

Practice: H5N1 vaccine formulations including a low haemagglutinin antigen dose and a non-aluminium adjuvant could be the best available option in the event of a avian H5N1 influenza pandemic.

Research: Further research was required to confirm the adverse event profile of non-aluminium-enhanced vaccines, particularly as the sample sizes of the trials included in this review were not sufficient to exclude the possibility of rare serious adverse events. Larger trials were required to verify the high immunogenicity of non-aluminium-enhanced vaccine formulations that used small quantities of haemagglutinin antigen.

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