Cold-adapted live influenza vaccine versus inactivated vaccine: systemic vaccine reactions, local and systemic antibody response, and vaccine efficacy. A meta-analysis

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Authors' objectives
To assess the differences between cold-adapted live influenza vaccine (AA-LIV) and inactivated influenza vaccine (IIV) in terms of systemic vaccine reactions, local and systemic antibody response and vaccine efficacy.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched from 1967 to 2000 using the following search algorithm: 'influenza' and 'vaccin*' and ('live' or 'cold adapted' or 'attenuated' or 'Ann Arbor' or 'intranasal'). In addition, the monthly Influenza Bibliography of the National Institute for Medical Research (Medical Research Council and WHO World Influenza Centre, London, UK) was searched manually from 1967 to 1992, and electronically from 1993 to 2000 via the NIMR website. Further trials were identified by examining the bibliographies from influenza textbooks, conference proceedings (e.g. Options for the Control of Influenza 1993, 1996, 2000), two current review articles on influenza vaccines, and cross-references of articles already selected. Publications in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials with a minimum of 10 participants per treatment arm were eligible for inclusion.

Specific interventions included in the review
Comparisons of AA-LIV and IIV influenza vaccine doses in adults or children were eligible for inclusion. Appropriate doses were defined as 7.5 to 15 microg haemagglutinin for IIV, (half of this amount for children), and 1E6.5 to 1E7.5 TCID 50 (50% tissue-culture infectious dose) for AA-LIV (1/10 dilution in children). In addition, the included studies had to have antigenic similarity of the influenza strains in the respective vaccines. The IIV vaccine type was given as whole virus, split (subvirion) or subunit (surface antigen). The placebo arms consisted of saline, uninfected allantoic fluid, or irrelevant influenza strain.

Participants included in the review
Adults or children of either gender who were receiving vaccination for influenza were eligible for inclusion. The age of the participants ranged from 1 to 90 years, and their health status ranged from apparently healthy to chronically ill, or was mixed.

Outcomes assessed in the review
The included studies had to report at least one of the following four outcomes: systemic vaccine reactions; systemic specific serum immunoglobulin (Ig)G antibody response; local (respiratory) specific IgA antibody response; and efficacy (protection from influenza), both experimentally and in the field (culture-positive illness within half a year following vaccination).

How were decisions on the relevance of primary studies made?
Two reviewers independently removed publications that did not meet the inclusion criteria. Any discrepancies were resolved by consensus.

Assessment of study quality
The authors state that a general score for study quality was not applied. It was believed that fulfilment of the selection criteria, in particular randomisation, indicated sufficient quality.
**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on: study, year and country of trial; the total number of participants; the age range and health state of the participants; whether AA-LIV booster vaccinations were performed; type of IIV vaccine and whether booster vaccinations were performed; whether the trial was double-blinded; whether the trial was placebo-controlled; whether the trial was approved; and the outcomes reported. The end points per trial, or in the case of antibody response and efficacy, per trial and influenza (sub)type (A-H3N2, A-H1N1, B), were tabulated. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

**How were the studies combined?**
The data were combined statistically in a meta-analysis using a random-effects model (see Other Publications of Related Interest no.1). This resulted in a pooled OR and 95% CIs. Publication bias was assessed using funnel plots.

**How were differences between studies investigated?**

Heterogeneity of the treatment effects was investigated using a weighted between-trial variance. When heterogeneity was found, sub-populations were investigated and the meta-analysis was repeated using a fixed-effect model (see Other Publications of Related Interest no.2); rate differences, instead of ORs, were used to check the robustness of the pooled results. A sensitivity analysis investigated the detection of possibly aberrant trials by excluding one trial at a time and observing whether the pooled result changed essentially.

**Results of the review**

Eighteen studies (n=5,000) were included in the review.

**Systemic vaccine reactions (11 trials).**

The proportion of systemic reactions varied considerably between trial arms (range: 0 to 31.6%). No significant differences between AA-LIV and IIV were found in any of the 11 studies, and the pooled OR was 0.96 (95% CI: 0.74, 1.24). Between-trial heterogeneity did not occur. The funnel plot gave no indication of publication bias.

**Systemic haemagglutination inhibition (HI) antibody response (8 trials).**

For influenza A-H3N2, data from 7 of the 8 trials showed that in all but one comparison, IIV-induced antibodies exceeded the protective HI-threshold after vaccination in approximately twice as many patients as AA-LIV did; the pooled OR was 0.17 (95% CI: 0.08, 0.33) favouring IIV. Heterogeneity between trials was large (p<0.001), apparently caused by between-trial differences in the pre-vaccination state. To eliminate heterogeneity caused through vaccination status, a subgroup analysis of seronegative participants was performed. This yielded a pooled OR of 0.07 (95% CI: 0.04, 0.15), with no significant heterogeneity (p=0.919).

For influenza A-H1N1, data from 10 trials found the percentages of patients exceeding the protective threshold for AA-LIV and IIV were closer than for A-H3N2, but the pooled OR was 0.41 (95% CI: 0.26, 0.67), which significantly favoured IIV. To eliminate heterogeneity caused through vaccination status, a subgroup analysis of seronegative participants was performed. This yielded a pooled OR virtually identical to that of A-H3N2, namely 0.09 (95% CI: 0.02, 0.33), with no significant heterogeneity (p=0.200).

For influenza B, data from 3 trials favoured IIV (83.3% versus 20.5%) and the pooled OR was 0.06, (95% CI: 0.02, 0.19). Between-trial heterogeneity was not found.

**Local IgA antibody response.**

Data from 4 trials on A-H3N2 found a stronger IgA induction by AA-LIV than IIV. Approximately half (52.4%) of the AA-LIV recipients, and a quarter (23.9%) of the IIV recipients responded to influenza A-H3N2 (pooled OR 5.54, 95%
CI: 2.48, 12.36). For A-H1N1, data from 4 trials showed that 52% of the AA-LIV recipients and 25.3% of the IIV recipients responded (pooled OR 4.61, 95% CI: 1.34, 15.85). For influenza B, data from 2 trials found that an IgA response occurred less frequently in both vaccine groups (AA-LIV, 20.7%; IIV, 7.4%), with an insignificant pooled OR of 2.46 (95% CI: 0.44, 13.75).

Culture-positive illness and vaccine efficacy.

For A-H3N2, 6 trials found an efficacy of 68.0% for AA-LIV and 78.2% for IIV; the pooled OR was 1.50 (95% CI: 0.80, 2.82). For A-H1N1, the result was 72.3% for AA-LIV and 72.5% for IIV, with a pooled OR of 1.03 (95% CI: 0.58, 1.82). For influenza B, the data from one trial yielded a vaccine efficacy of 100.0% and a OR of 1.00.

The robustness and sensitivity analysis showed these results to be stable. The funnel plot analysis did not indicate publication bias. Age did not apparently affect the OR values. Trials with a close match between vaccine strains and those with a mismatch showed similar OR-values, suggesting that neither vaccine offered an advantage in the case of antigenic drift.

Challenge success was greater with the experimental design (culture-positive illness in placebo group: 36.4 to 45.8%) than with the epidemic approach (1.8 to 6.8%; only in one trial was it greater, i.e. 25.6%). There were no significant differences between the OR values from either design. Vaccine efficacy was high for both vaccine types (50 to 100%), with the exception of two A-H1N1 trials performed in children and young adults previously unprimed for that subtype (16.7 to 49.4%).

Authors' conclusions

AA-LIV and IIV were similar with respect to (the prevention of) culture-positive influenza illness; AA-LIV did not offer any advantage over IIV with respect to protective efficacy. The design of the challenge study and age of vaccinees did not have a detectable influence. The intranasal route of vaccine administration can be better exploited by developing an inactivated vaccine that, by using special delivery systems or mucosal adjuvants, would be able to induce specific IgA at the mucosal surface of the airways.

CRD commentary

The review question and the study selection criteria were stated clearly. The literature search seemed reasonably comprehensive with a number of sources searched and no language restriction applied. The authors did not report any methods for assessing the validity of the included studies or for extracting the data. However, the range of statistical tests conducted seem to have been appropriate.

The presentation of the study's findings was not particularly clear, and the authors' conclusions do not seem to follow from the results presented and discussed.

Implications of the review for practice and research

Practice: The authors state that AA-LIV does not offer any advantage over IIV with respect to protective efficacy. The design of the challenge study and age of vaccinees did not have a detectable influence. The intranasal route of vaccine administration can be better exploited by developing an inactivated vaccine that, by using special delivery systems or mucosal adjuvants, would be able to induce specific IgA at the mucosal surface of the airways. The authors also stated their concerns about the widespread use of any LIV, in order to exclude even the theoretical possibility of the emergence of a pandemic influenza virus involving a live-virus vaccine.

Research: The authors discussed current research taking place, but did not offer any implications for future research.

Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adaptation, Physiological; Administration, Intranasal; Adolescent; Adult; Aged; Antibodies, Viral /blood; Child; Child, Preschool; Cold Temperature; Humans; Immunoglobulin A /blood; Infant; Influenza Vaccines /administration & dosage /adverse effects /immunology; Influenza, Human /prevention & control; Injections, Intramuscular; Middle Aged; Vaccines, Inactivated /immunology

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.