Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines


CRD summary
This generally well-conducted review found that 2009 H1N1 vaccines achieved adequate immunogenicity; serious adverse events after vaccination were rare. Oil-in-water adjuvant vaccines gave the highest protection after a single low dose, but they had most frequent mild to moderate adverse events. The authors' conclusions (except those for mild to moderate adverse events) are likely to be reliable.

Authors' objectives
To review the efficacy and safety of various influenza A 2009 H1N1 vaccine formulations.

Searching
MEDLINE (from 2009 onwards), EMBASE, and nine clinical trial registries were searched up to April 2011 for relevant studies published in any language. Search terms were reported. A manual search of references of articles was performed.

Study selection
Studies that evaluated the influenza A 2009 H1N1 vaccine safety and immunogenicity in healthy children, adolescents, adults and elderly participants who had not previously been vaccinated with H1N1 vaccines were eligible for inclusion. All study designs were eligible for inclusion, but the main analysis was based on randomised controlled trials (RCTs) only. The primary outcome was the seroconversion rate according to haemagglutination inhibition; it appears that if this was not available, the sero-response rate was used. Secondary outcomes were adverse events.

The included trials were conducted in Europe, Asia, Australia, North America and one in Central America. Participants ranged from 0.5 to 93 years old. The vaccines used included inactivated, surface-antigen; inactivated, split virus; live-attenuated whole virus; and intranasal, whole virus vaccines. Where reported, the doses ranged from 1.875 to 30μg of haemagglutinin antigen. Aluminium and other adjuvants were used. Outcomes extracted were haemagglutination inhibition, fever, pain and other local and systemic adverse effects.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Quality was assessed for all RCTs based on: randomisation (sequence generation and allocation concealment); blinding; and adequacy of analyses. One point was given for each criteria that was adequately met up to a maximum of 3 points. The effect of trial quality on the results was investigated by dichotomising trials according risk of bias. Definitions of these were given in the review.

Two reviewers independently assessed trial quality.

Data extraction
Data were extracted to calculate risk ratios (RR) and 95% confidence intervals (CI) for each outcome. When both seroconversion and sero-response data were available in a trial, only seroconversion data were used. When it was not possible to extract some outcomes from a trial, the corresponding author was contacted.

Two reviewers independently performed the data extraction.

Methods of synthesis
Random-effects meta-analysis was used to pool the results; these were compared with results from fixed-effect models. Comparisons were made of various formulations in head-to-head comparisons, and a comparison of adjuvanted with non-adjuvanted vaccines. Statistical heterogeneity was assessed using I².
Multiple-treatments meta-analysis was also used for the primary outcome, resulting in the estimation of pooled odds ratios (OR) and risk differences (RD) with 95% credibility intervals.

Sensitivity analysis of all evidence (including from non-randomised studies), combining data from single arms, was performed. All analyses were performed twice, based on results after one dose only and then on results after both vaccine doses. An additional proportion meta-analysis was performed to estimate the pooled effect of the absolute percentage of participants who benefited from the second dose. Subgroup analyses were based on the following age groups; children from six months to nine years; adolescents from 10 to 17 years; adults from 18 to 64 years; and elderly participants 65 years or older.

**Results of the review**

Eighteen RCTs (16,725 participants) were included in the review. Ten trials had the maximum score for quality, four scored 2 points, six trials scored 1 point, and two trials scored zero. Only two RCTs were double blinded.

**Immunogenicity:** Among participants who received only one dose of flu vaccine, rates of seroconversion were higher with higher versus lower doses of haemagglutinin antigen, and the effect was similar for non-adjuvanted vaccines (RR 1.05, 95% CI 1.03 to 1.07; 12 RCTs) and adjuvanted vaccines (RR 1.10, 95% CI 1.04 to 1.17; four RCTs). Among participants who received two doses of flu vaccine, rates of seroconversion were similar, irrespective of dose. For adolescent, adult and older participants, an additional dose was of no extra benefit; however, for children, the second dose substantially increased seroconversion for all vaccine types other than high-dose non-adjuvanted vaccines. The use of aluminium as a vaccine adjuvant did not provide a benefit at any age; data for investigating other adjuvants were scarce. Multiple-treatments meta-analysis indicated that vaccine formulations including oil-in-water adjuvants at a dose of 1.88 to 5.25µg showed significantly higher immunogenicity than all non-adjuvanted and aluminium-adjuvanted vaccine preparations.

**Adverse events:** The rate of serious flu vaccine-related adverse events was low. Three serious vaccine-related adverse events were reported out of 22,826 vaccinated participants in 32 comparisons; all symptoms were resolved in 10 days. Mild to moderate adverse reactions were common: rates of fever ranged from 0 to 15%; local pain from 7% to 84%; any systemic symptom from 1% to 84%; and any local symptom from 0 to 57% (where reported). Formulations including oil-in-water adjuvants showed the highest rates of pain and any local and systemic adverse events. Non-adjuvanted vaccines showed a moderate dose-response for all adverse events. There was no evidence of a higher risk of adverse events in people who received two rather than one dose.

**Authors’ conclusions**

After two doses, all 2009 H1N1 influenza vaccines achieved adequate immunogenicity. Several one-dose formulations might be valid for future vaccines, but two doses may be needed for children, especially when a low-dose non-adjuvanted vaccine was used. Vaccines with oil-in-water adjuvants were more immunogenic than either non-adjuvanted or aluminium-adjuvanted vaccines at equal doses. Higher doses were slightly more immunogenic in non-adjuvanted formulations, especially for the children and elderly participants. The rate of serious vaccine-related adverse events was low, but mild to moderate adverse reactions were more common for oil-in-water adjuvanted vaccines.

**CRD commentary**

The review question was clear. Inclusion criteria were broad, but clear. Several databases were searched with no language limitations. Although the authors searched trial registries in an attempt to identify unpublished trials, they found that under one third of trials identified on the trial registers were identified in the search for published studies, so publication bias may have affected the results. The processes of quality assessment and data extraction were performed in duplicate, which reduced the chance of error or bias; this was not done for the study selection stage.

Quality of included trials was assessed using appropriate criteria and the results were used in the analysis. The meta-analysis methods appear appropriate, but not all results for the methods that the authors stated that they used were reported. Results of the assessment of heterogeneity were not reported. The authors acknowledged that the mild to moderate adverse events results were based on a subset of trials, and may not be reliable.

This was a generally well-conducted review, although the reporting was unclear in some areas. The authors’ conclusions (other than those relating to mild to moderate adverse events) are likely to be reliable.
Implications of the review for practice and research

Practice: The authors stated that, during an epidemic, vaccines with oil-in-water adjuvants may represent the best option, as they induce the highest protection after a single, low dose. In non-epidemic situations, non-adjuvanted vaccines may be useful, at a dose of 20μg or over, especially for elderly people and children.

Research: The authors stated that future trials sponsored by non-industry agencies were needed that compared vaccines using different types of adjuvants and oil-in-water adjuvants produced by different companies. They recommended that vaccine safety should be further investigated in large observational studies. They also stated that further studies of live-attenuated vaccines were needed, as haemagglutination-inhibition may not be a good marker of protection for these vaccines.

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