A systematic review of intradermal influenza vaccines

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CRD summary
The review concluded that intradermal and intramuscular administration of influenza vaccines had comparable efficacy in both younger and older adults. There were higher rates of local adverse events such as erythema, swelling, induration and pruritis with intradermal administration. Limitations in the evidence base and potential for bias in the review mean that the authors' conclusions should be considered tentative.

Authors' objectives
To evaluate the efficacy of immunogenicity and safety of intradermal influenza vaccines compared with traditional methods of administration (intramuscular or subcutaneous) in the general population and older adults.

Searching
EMBASE and PubMed were searched from 1950 to May 2011 for relevant studies published in English; limited search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared intradermal administration of seasonal split virus influenza vaccines with intramuscular or subcutaneous administration in adults (18 years or older) were eligible for the review. Outcomes of interest included antibody response by the haemagglutinin inhibition method which reported results as geometric mean titre (GMT), geometric mean titre ratio (GMTR), seroprotection rate and seroconversion or significant increase rate (definitions reported in the review) assessed at 21 to 28 days post vaccination. Studies that investigated pandemic or whole virus vaccines or studies of immunocompromised participants were excluded.

The included studies had separate analyses for participants aged up to 60 years and those aged more than 60. Doses of the intradermal influenza vaccine varied: five trials included a 3mcg dose group, five trials included a 6mcg dose group, four trials included a 9mcg group, three trials included a 15mcg group and one trial included a 21mcg group. Most trials used the intramuscular form of administration in the control groups; one trial included either intramuscular or subcutaneous administration as control. All trials used a dose of 15mcg in the control groups.

Two reviewers independently selected studies for the review using separate standardised forms.

Assessment of study quality
Studies were assessed for quality using the Jadad scale of randomisation, blinding and withdrawals and drop-outs.

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Data extraction
Data were extracted on the outcomes, geometric mean titre ratio, seroconversion rate, seroprotection rate, local and systemic adverse events, each with corresponding 95% confidence intervals (CIs), for the three influenza strains A/H1N1, A/H3N2 and B.

The authors did not state how many reviewers extracted data for the review.

Methods of synthesis
Results were synthesised in narrative format and included in tables. Results were grouped separately for participants aged 18 to 60 years and participants aged over 60.

Results of the review
Thirteen RCTs (13,515 patients) were included in the review. Seven trials were undertaken in adults aged 18 to 60 years, four trials were undertaken in adults aged more than 60 years, one trial did separate analyses for older and younger participants (≤60 years and >60 years) and one trial did a separate analysis for older adults only (>60 years).
Nine trials had an overall Jadad score of 3 and four trials had an overall Jadad score of 1. No trials were double blinded.

**Efficacy in patients 18 to 60 years old:** In seven out of eight studies, geometric mean titre ratio, seroconversion rates and seroprotection rates were comparable between groups. In one study, patients with intramuscular vaccines had significantly higher geometric mean titre ratio, seroconversion rates and seroprotection rates than patients with intradermal vaccines; this was except for seroconversion rates for H1N1 and H3N2 strains in those with a pre-vaccination titre less than 10 and seroprotection rate for H1N1.

**Efficacy in patients more than 60 years of age:** In four out of six studies, geometric mean titre ratio, seroconversion rates and seroprotection rates were comparable between groups. In two studies, compared to the intramuscular group the intradermal group had significantly higher geometric mean titre ratio, seroconversion and protection rates.

**Safety:** In all studies, rates of adverse events in the first three days were generally comparable between intradermal and intramuscular vaccine administration. In 13 studies, some local adverse events that occurred within the first seven days, such as erythema, swelling, induration and pruritis, were significantly more frequent in the intradermal group when compared to the intramuscular group. There was no evidence of a difference in the rates of ecchymosis or pain at the injection site between groups.

**Authors’ conclusions**
There was comparable efficacy between intradermal and intramuscular administration of influenza vaccine in the 18 to 60-year-old population and comparable or superior efficacy of intradermal compared with intramuscular administration in the more than 60-year-old population. Rates of local adverse events within the first seven days, such as erythema, swelling, induration and pruritis, were consistently higher in the intradermal group. Rates of adverse events within the first three days were generally comparable.

**CRD commentary**
The review addressed a clear research question supported by appropriate inclusion criteria. The search was limited to two electronic databases but covered a wide publication date range. No specific attempts were made to find unpublished studies and only studies in English language were considered, so publication and language biases could not be ruled out. Appropriate methods were used to select studies and assess studies for quality; the authors did not state how many reviewers extracted data so reviewer error and bias could not be excluded. A valid tool was used for quality assessment but the included studies were of limited quality and none were blinded.

Clinical differences in the doses of the intradermal vaccine meant that the synthesis of studies in narrative format was appropriate. The authors acknowledged that the outcomes assessed did not necessarily correlate well with clinical outcomes such as reduction in influenza rates, hospitalisations and mortality, which were not measured in the included studies.

Limitations in the evidence base and potential for bias in the review mean that the authors’ conclusions should be considered tentative.

**Implications of the review for practice and research**
**Practice:** The authors stated that, given comparable efficacy between reduced dose intradermal administration and full dose intramuscular administration of influenza vaccines, intradermal administration may increase the availability of the vaccine to a greater number of people in situations of short supply.

**Research:** The authors did not state any implications for research.

**Funding**
Not stated.

**Bibliographic details**
Young F, Marra F. A systematic review of intradermal influenza vaccines. Vaccine 2011; 29(48): 8788-8801

**PubMedID**
21968444
Record Status
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.