Physical interventions and injection techniques for reducing injection pain during routine childhood immunizations: systematic review of randomized controlled trials and quasi-randomized controlled trials

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CRD summary
The authors concluded that pain during childhood injection vaccination can be reduced by use of less painful brands of vaccine injections, positioning children upright and stroking the skin close to the injection site and performing intramuscular injections rapidly without aspiration. The authors’ conclusions were based on limited and generally poor-quality evidence and so their reliability is unclear.

Authors’ objectives
To assess the effectiveness of physical interventions and injection techniques on pain reduction during vaccine injection in children.

Searching
MEDLINE (from 1950), EMBASE (from 1980), CINAHL (from 1982) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to 2008 for published articles and academic theses in any language. Search terms were reported. Reference lists of retrieved articles were searched manually and experts in the field were contacted. Abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) or quasi-RCTs that assessed the effects of 12 clearly defined injection methods on pain or distress experienced by children aged zero to 18 years who underwent vaccination by injection in any hospital or community setting were eligible for inclusion. Eligible studies were required to use a validated technique (self-report by the child or observation by others) to measure pain or distress either within five minutes of vaccination or after the last injection if multiple injections were administered.

Included studies were conducted in USA, Canada, Europe and Australia. Included studies evaluated the effects of: different vaccine formulations; position of child; injection route; skin cooling; skin stroking; vaccine order; vaccine sequence; vaccine temperature; and rapid intramuscular injection without aspiration. Outcome measures were assessed by the children themselves and/or others (parent, nurse, physician, observer) with a variety of measurement scales.

Two reviewers screened studies for inclusion.

Assessment of study quality
Two reviewers assessed the quality of the included studies according to the Cochrane Collaboration’s Risk of Bias tool with criteria on: sequence generation; allocation concealment; blinding; completeness of outcome data; selective outcome reporting; and other potential bias. Each study was rated overall as being at low, high or unclear risk of bias. Discrepancies were resolved by consensus or referral to a third reviewer if necessary.

Data extraction
Two reviewers independently extracted means and standard deviations (SDs) to calculate mean differences and 95% confidence intervals (CIs) for continuous outcomes. Categorical data were extracted to calculate relative risks (RRs) and risk differences (RDs). Data were extracted on an intention-to-treat (ITT) basis or per-protocol. Primary authors were contacted for further details where necessary.

Disagreements were resolved through discussion or by referral to a third reviewer if necessary.

Methods of synthesis
Mean differences and 95% CIs were combined to calculate weighted mean differences (WMDs) or standardised mean differences (SMDs). Relative risks and risk differences were combined using a fixed-effects model. The number needed to treat (NNT) was calculated. Data for child and parent assessments were reported separately from other assessors.

Statistical heterogeneity was assessed with the $I^2$ statistic and $X^2$ test. Where statistical heterogeneity was evident, a priori subgroup analysis was planned based on age. Where meta-analysis was not possible, data were presented as a narrative synthesis. Where appropriate, sensitivity analysis was performed by exclusion of studies at high risk of bias.

Publication bias was assessed through visual inspection of funnel plots.

**Results of the review**

Nineteen studies (n=2,814, range 31 to 623) were included in the review. Seventeen studies were included in the meta-analysis. Six studies were at low risk of bias, five were at high risk of bias and risk of bias in remaining eight studies was unclear.

**Injection of different formulations of the same vaccine (five studies):** Priorix injection caused less pain than the M-MR II vaccine according to children's self-report (SMD -0.66, 95% CI -0.81 to -0.50, NNT=3.7; two studies) and resulted in less crying (RR 0.66, 95% CI 0.59 to 0.74, $I^2=48\%$, NNT=3.2; three studies). Similar findings were found for parental report studies (three studies) and physician-reported scores, but there was some evidence of statistical heterogeneity.

**Position of the child during injection (four studies):** Significant heterogeneity was found ($I^2=65\%$). The authors reported that three studies showed greater pain scores in children lying supine during vaccination compared with children who were sitting or being held by a parent. A forest plot showed that the difference was only statistically significant in two studies.

**Stroking the skin close to the injection site before and during injection (one study):** Children who received stroking reported less pain than those who did not receive stroking.

**Order of vaccine injection when two vaccines were administered sequentially (one study):** Overall, pain was reported to be lower in children who received diphtheria-polio-tetanus-acellular pertussis-Haemophilus influenzae type b (DPTaP-Hib) vaccine first and pneumococcal conjugate vaccines (PCV) second compared to children who received the vaccines in the opposite order.

**Rapid injection without aspiration for intramuscular injection (one study):** Rapid injection without aspiration was found to be less painful as assessed by observers, cry duration and parent and physician assessment.

Insufficient evidence was found to support greater effectiveness for intramuscular versus subcutaneous injection (three studies), cooling the skin at the injection site with ice before injection (two studies), simultaneous versus sequential injection of two vaccines (one study) and vaccine temperature (one study).

Sensitivity analysis was not performed. The authors reported potential for publication bias.

**Authors' conclusions**

Pain can be reduced in children receiving vaccine injections by administering brands of vaccines that are less painful, positioning or holding children upright, stroking the skin close to the injection site before and during injection, administering the least painful vaccine first when two vaccines are to be injected sequentially and performing intramuscular injections rapidly without aspiration.

**CRD commentary**

The review question and inclusion criteria were clearly defined. The literature search was adequate and was not restricted by language. However, no attempts were made to locate unpublished data, which meant that potentially relevant papers may have been missed. The authors acknowledged potential for publication bias. The authors performed
an appropriate validity assessment. Study quality was generally poor or unclear; this was not investigated as part of the data synthesis. The authors undertook each stage of the process in duplicate, which minimised risks of reviewer error and bias. A fixed-effects model may not have been appropriate given the presence of statistical heterogeneity for some comparisons. No further investigations through sensitivity analysis were reported. The authors acknowledged certain limitations with the included studies, such as small number of studies and participants, limited number of vaccines, low quality ratings, variability in pain assessment and missing summary statistics for a few trials.

The evidence was generally based on a small number of studies, outcomes were diverse and often measured using indirect observations and studies were generally of poor quality, which made the reliability of the authors’ conclusions unclear.

### Implications of the review for practice and research

**Practice:** The authors stated that changing the temperature of vaccines would not be recommended and use of aspiration before intramuscular injection of vaccines should be avoided.

**Research:** The authors stated that further research was needed into the effects on pain after vaccine injection for: route of administration; ice in selected age groups; stroking the skin; vaccine order; injection speed; injection site; and needle characteristics.

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