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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ABSTRACT

Background: Vaccine injections are the most common reason for iatrogenic pain in childhood. With the steadily increasing number of recommended vaccinations, there has been a concomitant increase in concern regarding the adequacy of pain management. Physical interventions and injection techniques that minimize pain during vaccine injection offer an advantage over other techniques because they can be easily incorporated into clinical practice without added cost or time. Their effectiveness, however, has not previously been studied using a systematic approach.

Objective: The purpose of this review was to determine the effectiveness of physical interventions and injection techniques for reducing pain during vaccine injection in children.

Methods: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials databases were searched to identify randomized controlled trials (RCTs) and quasi-RCTs that determined the effect of physical interventions and injection techniques on pain during injection of vaccines in children 0 to 18 years of age, using validated child self-reported pain or assessments of child distress or pain made by others (parent, nurse, physician, observer). We sought to determine the effects of: (1) different formulations of the same vaccine; (2) position of the child during injection; (3) intramuscular versus subcutaneous injection; (4) cooling of the skin at the injection site with ice before injection; (5) stroking the skin or applying pressure close to the injection site before and during injection; (6) order of vaccine injection when 2 vaccines were administered sequentially; (7) simultaneous versus sequential injection of 2 vaccines; (8) vaccine temperature; (9) aspiration before injection; (10) anatomic location of injection; (11) aspects of the needle (gauge, length, angle of insertion, speed of injection); and (12) combinations of these interventions. All meta-analyses were performed using a fixed-effects model.

Results: Nineteen RCTs involving 2814 infants and children (0–18 years of age) were included in the systematic review. One study included children ≥16 years and adults (n = 150). Interventions with positive findings are summarized here. In 2 trials that used child self-reports of pain during administration of measles-mumps-rubella vaccine (total, 680 children with complete data), the Priorix vaccine caused less pain than the M-M-R_{II} vaccine (standardized mean difference [SMD],

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–0.66; 95% CI, –0.81 to –0.50; $P < 0.001$). In 3 trials (404 children), the number needed to treat (NNT) with Priorix to prevent 1 child from crying was 3.2 (95% CI, 2.6–4.2). In 4 trials (281 infants and children), sitting children up or having parents hold infants appeared to cause less pain than the supine position, but the difference was not statistically significant; however, significant heterogeneity was found among the studies, and a qualitative approach was used for data analysis. A benefit was observed for 3 of the 4 studies; the SMD ranged from –0.4 to –0.8 ($P < 0.05$ for all analyses). The negative findings observed for the remaining study may have been the result of methodologic heterogeneity. Stroking the skin close to the injection site before and during injection reduced pain in 1 trial (66 children; SMD, –0.53; $P = 0.03$). One study (120 children) found that when diphtheria-polio-tetanus-acellular pertussis-*Haemophilus influenzae* type b (DPTaP-Hib; Pentacel) and pneumococcus (Prevnar) were injected sequentially during the same office visit, observer- and parent-reported pain scores were lower when DPTaP-Hib was injected first (SMD, –0.40 and –0.57, respectively; $P \leq 0.03$). In 1 study (113 infants) comparing rapid intramuscular injection without aspiration and slow intramuscular injection with aspiration, the rapid injection without aspiration was associated with less pain (SMD, –0.62 to –0.97 for parent, nurse, physician, and observer behavioral pain ratings; all, $P < 0.05$). The NNT to prevent 1 infant from crying was 2.5 (95% CI, 1.8–4.3).

Conclusions: Pain during immunization can be decreased by: (1) injecting the least painful formulation of a vaccine; (2) having the child sit up (or holding an infant); (3) stroking the skin or applying pressure close to the injection site before and during injection; (4) injecting the least painful vaccine first when 2 vaccines are being administered sequentially during a single office visit; and (5) performing a rapid intramuscular injection without aspiration. (*Clin Ther.* 2009;31[Suppl B]: S48–S76) © 2009 Excerpta Medica Inc.

Key words: infant/child, pain management, vaccine, immunization, systematic review, physical interventions, injection techniques.

INTRODUCTION

Most vaccines are administered by needle injection through the skin, a drug delivery system that is distressing for children, their families, and health care workers. There has been increasing attention paid to the issue of pain management during vaccine injections in childhood, and an accumulating body of research has investigated the effectiveness of various analgesic modalities.[1]

Physical interventions and injection techniques designed to reduce pain during vaccine injection are an attractive option for pain management because they add little or no time or cost to the procedure. In a recent audit of immunization pain management, however, few physicians reported using pain-relieving physical interventions or injection techniques in clinical practice.[2] The objectives of this study were to systematically review the effectiveness of various physical interventions and injection techniques for reducing vaccine injection pain in children, to inform clinicians regarding best practices and to identify areas that need additional research.

We sought trials that determined the effects of the following interventions on vaccine injection pain in children 0 to 18 years of age: (1) different formulations of the same vaccine; (2) position of the child during injection; (3) intramuscular versus subcutaneous injection; (4) cooling of the skin at the injection site with ice before injection; (5) stroking the skin or applying pressure close to the injection site before and during injection; (6) order of vaccine injection when 2 vaccines were administered sequentially; (7) simultaneous versus sequential injection of 2 vaccines; (8) vaccine temperature; (9) aspiration during injection; (10) anatomic location of injection; (11) aspects of the needle (gauge, length, angle of insertion, speed of injection); and (12) combinations of these interventions.

MATERIALS AND METHODS

Literature Search

Searches were performed using the OVID search platform in the following databases: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials. No language restrictions were applied. Search terms used to identify studies for inclusion were determined by the authors based on their content expertise in this area in consultation with the chief librarian (Elizabeth Uleryk) at The Hospital for Sick Children (Toronto, Ontario, Canada), who conducted the searches. A summary of the strategies used for the various databases is provided in the **appendix**.

The titles and abstracts of all retrieved citations were printed and scanned by 2 reviewers (A.T. and

V.S.). The reviewers identified citations to be retrieved as full articles, and these were assessed for eligibility by 2 reviewers (A.T. and A.K.). Additional studies were identified by reviewing the reference lists in the retrieved articles. Reviewers were not blinded to the authors or settings of the studies in the scanned articles. Experts in the field were contacted to identify additional articles.

Study Selection

Inclusion Criteria

The review included: (1) children 0 to 18 years of age undergoing immunization with a vaccine that required injection in any setting (hospital or community); (2) randomized controlled trials (RCTs) or studies with a quasi-randomized study design, whereby the effect of a specific injection method was determined; and (3) outcomes (pain or distress experienced by the child) were obtained within 5 minutes of the vaccine injection using validated techniques. We included studies that were published as full reports or short reports, as well as published academic theses. We noted whether studies included information regarding approval from institutional review boards (IRBs) and ethics committees (ECs), but we did not exclude studies on this basis because we anticipated retrieval of studies that were published before scientific journals routinely included such information and we wanted to maximize the number of included studies.

Exclusion Criteria

Studies in which the analgesic intervention or the outcome of interest was not clearly defined were excluded. We also excluded published abstracts, letters, commentaries, and editorials.

Primary Outcome

The primary outcome was the pain or distress experienced by the child during *vaccine injection* (defined as needle puncture through the skin and injection of vaccine material), as assessed by the child using validated tools (self-report), or by others (parent, nurse, physician, or observer) using validated observational tools. Examples of validated self-report measures included: visual analog scale (VAS), Faces Pain Scale–Revised (FPS–R),[3] Oucher Scale,[4] and Faces Pain Scale (FPS).[5] Examples of validated observational measures included: Modified Behavioral Pain Scale (MBPS),[6] VAS, cry duration, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS),[7] Child–Adult Medical Procedure Interaction Scale–Short Form,[8] and Observational Scale of Behavioral Distress–Revised (OSBD–R).[9] Outcomes were recorded according to established methods up to 5 minutes after vaccine injection (or after the last injection if multiple injections were administered).

Validity Assessment

The included trials were not masked to the reviewers. The methodologic quality of the studies was assessed by 2 reviewers (A.T. and A.L.I.) using the Cochrane Collaboration's "Risk of Bias" tool.[10] The included domains were: sequence generation, allocation concealment, blinding of outcome assessors and patients, completeness of outcome data, selective outcome reporting, and other potential biases. Methodologic quality criteria were assessed using: *yes* (low risk of bias), *no* (high risk of bias), and *unclear* (lack of information or uncertainty over the potential for bias). Discrepancies were resolved by consensus and with the assistance of a third reviewer (V.S.), if necessary. Studies from 2 of the authors (M.I. and A.T.) were also assessed.

Data Abstraction

Data from each eligible study were extracted individually by 2 reviewers (A.T. and A.L.I.) using custom-made (specific for injection technique intervention) data-collection forms, and the results were compared. The reviewers resolved any disagreements through discussion or, if required, consultation with a third person (V.S.). Modification of original data was done as needed on a predefined, restricted basis and according to established methods such as those reported by Hozo et al.[11] For example, means (SDs) were calculated from medians, ranges, and 95% CIs. Data were abstracted using an intent-to-treat (ITT) approach; however, if ITT results were not available, a per-protocol approach was used for data presentation.

Study Characteristics

We included randomized and quasi-randomized studies of ≥1 physical intervention or injection technique compared with a placebo, no intervention, or another technique for pain management during needle puncture and vaccine injection in children 0 to 18 years of age. Outcome measures included pain or distress, as assessed by the children themselves and/or

by others (parent, nurse, physician, observer) using validated tools, as specified under Primary Outcome.

Clinical heterogeneity was assessed by noting the differences among studies in the following variables: age group (population), country, intervention, type of vaccine, injection method, simultaneous use of other pain-reducing strategies, and outcome assessments.

Data Synthesis

Data synthesis was performed using qualitative and quantitative (meta-analytic) methods. All statistical analyses were conducted using Review Manager (RevMan) version 5.0, the statistical software provided by the Cochrane Collaboration (Copenhagen, Denmark).[10] Data were combined for outcomes that were measured using the same tool, regardless of the rater who performed the assessment (eg, nurse, physician, observer), except for child and parent assessments, which were reported separately. If data were available for multiple raters using the same tool, the scores were aggregated for the same rater(s).

For continuous data, mean differences (MDs) and weighted MDs (WMDs) were calculated along with 95% CIs. Standardized MDs (SMDs) and 95% CIs were also computed by combining the results from different tools measuring the same construct (pain) or from individual studies to standardize results of studies to a uniform scale. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. Values were rated as follows: <0.40, small; 0.40 to 0.70, moderate; and >0.70, large.[10] For categorical data, relative risks (RRs) and risk differences (RDs) were reported. The number needed to treat (NNT) was determined. All meta-analyses were performed using a fixed-effects model.[10]

We attempted to contact authors of trials for original data if the published report did not contain descriptive data (ie, means, SDs). Missing data were not imputed. When descriptive data were not provided, a summary of the findings, as reported by the authors, was included in the review.

Study heterogeneity was assessed using I^2 and χ^2 tests. For I^2, the following template was used to judge the results regarding heterogeneity: 0% to 40%, may not be important; 30% to 60%, may be moderate; 50% to 90%, may be substantial; and 75% to 100%, may be considerable. For all I^2 values >40%, the magnitude and accompanying P value from the χ^2 test were considered in the overall interpretation.[10] We planned a priori subgroup or single-study analyses based on child age (ie, younger vs older children, as determined by the child's ability to provide self-reports) if heterogeneity was judged considerable.

If appropriate, a sensitivity analysis was performed by including and excluding studies with high likelihood of bias, as assessed by the Risk of Bias tool.[10] Funnel plots were performed to assess for the possibility of publication bias if there were sufficient trials (>10).[10]

RESULTS

The literature search yielded 1790 references from the 4 databases (**Figure 1**). All references were saved in an EndNote library that identified 323 duplicates. The remaining 1467 references were reviewed by 2 of the authors (A.T. and V.S.) against the inclusion criteria.

Nineteen trials met the inclusion criteria for the systematic review. They were classified as follows: (1) injection of different formulations (interchangeable brands) of the same vaccine (n = 5)[12–16]; (2) position of the child during injection (n = 4)[17–20]; (3) injection into different tissues (intramuscular vs subcutaneous; n = 3)[21–23]; (4) cooling the skin at the injection site with ice before injection (n = 2)[24,25]; (5) stroking the skin close to the injection site before and during injection (n = 1)[26] (a duplicate publication[27] was not included in the review); (6) order of vaccine injection when 2 vaccines were administered sequentially (n = 1)[28]; (7) simultaneous versus sequential injection of 2 vaccines (n = 1)[29]; (8) vaccine temperature (n = 1)[30]; and (9) combined injection technique (rapid intramuscular injection without aspiration) (n = 1).[31] Four of the 19 included studies[15,17,22,24] did not contain information about IRB/EC approval or informed consent. None of the included studies evaluated specific aspects of the needle (gauge, length, angle of insertion, or speed of injection) or the anatomic location of the injection (arm, leg, or buttock).

Pain and distress were assessed in the included studies using various tools: CHEOPS (range 4–13),[7] FPS (range, 0–100, 0–10, or 0–5),[5] Parent Faces Pain Scale (a separate scale constructed by the investigators for the study; range, 0–4),[21] Facial Grimace Scale (range, 0–300),[18] FPS–R (range, 0–100),[3] Global Mood Scale (range, 1–7),[32] MBPS (range, 0–10),[6] McGill Present Pain Intensity Questionnaire (range, 0–5),[33] Oucher Scale (range, 0–100 or 0–5),[4] OSBD–R (range, not reported [NR]),[9] and VAS (range, 0–100 mm or 0–10 cm).

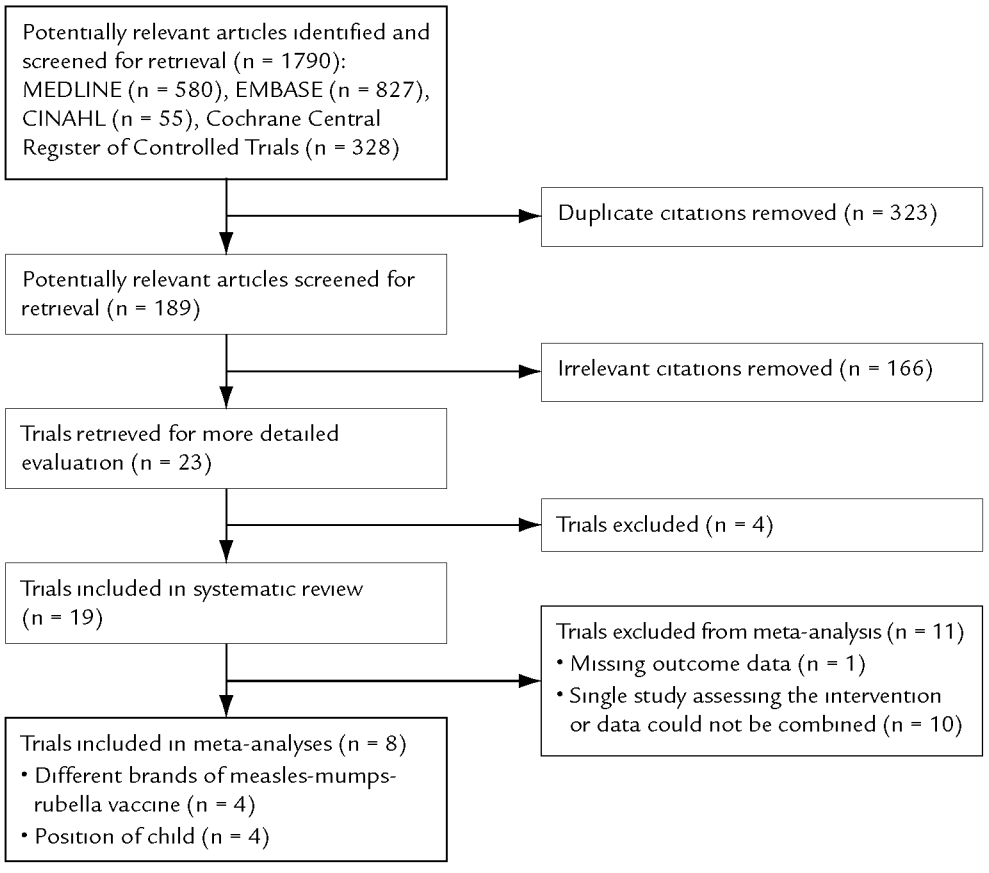

Figure 1. Flow diagram for included trials.

Characteristics of the included trials, which involved 2814 infants and children (0–18 years of age), are provided in **Table I.**[12–26,28–31] One study[30] included children ≥16 years and adults (n = 150). Results of methodologic quality (Risk of Bias) assessments of the included studies are presented in **Table II.**[12–26,28–31] The percent agreement on all key items for all of the 19 included studies was 79%. Disagreements were resolved by consensus (A.T. and A.L.I.).

Injection of Different Formulations of the Same Vaccine

The pain caused by different brands of measles-mumps-rubella vaccine was evaluated in 5 trials[12–16] (**Table I**); 4 of the trials compared Priorix* and M-M-R_{II}† (or RORVax,‡ the equivalent of M-M-R_{II})[12–14,16] and 1 trial compared Pluserix (no longer available commercially) and M-M-R_{II}.[15] The overall risk of bias was low in 3 of the trials,[12,13,15] unclear in 1 trial,[16] and high in 1 trial[14] (**Table II**).

Children's self-reported pain ratings could be combined for 2 studies that included 680 children undergoing vaccination with Priorix or M-M-R_{II} (outcome data were missing for 3 children).[13,16] The SMD was –0.66 (95% CI, –0.81 to –0.50; $P < 0.001$). No evidence of heterogeneity was observed for this outcome. In a study that reported on the incidence of pain (FPS–R score ≥4 on a scale of 0–10) versus no pain (score of 0),[16] the RR was 0.40 (95%

*Trademark: Priorix (SmithKline Beecham Pharma, Oakville, Ontario, Canada; and GlaxoSmithKline, Brentford, Middlesex, United Kingdom).

†Trademark: M-M-R_{II} (Merck Frosst Canada & Co., Montreal, Quebec, Canada).

‡Trademark: RORVax (Aventis Pasteur–MSD, Lyon, France).

Table I. Characteristics of the trials included in the systematic review (N = 19).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Different Formulations of the Same Vaccine for Measles-Mumps-Rubella						
Ipp et al,[12] 2004, Canada	Vaccine formulation	Yes	N = 49; infants 12 mo; single center, primary care practice	Chronic illness; immune deficiency; immunosuppression; history of anaphylaxis to egg protein; fever; acute illness preventing injection	Priorix (n = 26) or M-M-R_{II} (n = 23); 0.5 mL SC; 25-gauge, 15-mm needle; deltoid muscle	Observer MBPS, parent VAS, physician VAS, cry
Ipp et al,[13] 2006, Canada	Vaccine formulation	Yes	N = 60; children 4–6 y; single center, primary care practice	NR	Priorix (n = 30) or M-M-R_{II} (n = 30); 0.5 mL SC	Child Oucher Scale, parent VAS, physician VAS, cry
Knutsson et al,[14] 2006, Sweden	Vaccine formulation	Yes	N = 295; infants 18–24 mo; single center, Child Health Centre	NR	Priorix (n = 143) or M-M-R_{II} (n = 152); 0.5 mL SC; 0.4-mm × 19-mm needle; middle lateral side of left thigh muscle, ≥15 sec	Observer CHEOPS, parent VAS
Lyons and Howell,[15] 1991, Ireland	Vaccine formulation	No	N = 77; children 44 mo; single center	NR	Pluserix (n = 37) or M-M-R_{II} (n = 40); 0.5 mL SC; 25-gauge needle; deltoid muscle	Cry

(continued)

Table I (continued).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Wood et al,[16] 2004, France	Vaccine formulation	Yes	N = 623; children 4–6 y; multicenter, primary care practice	History of measles, mumps, or rubella; exposure to one of the viruses within past 42 days; allergy to vaccine, egg protein, or neomycin; concomitant vaccine injection; previously given 2nd measles-mumps-rubella dose; immunosuppressive or immunoglobulin therapy; immune disorder; congenital disease; acute illness; or blood products within past 3 mo	Priorix (n = 311) or RORVax (n = 312); 0.5 mL SC; nondominant upper arm	Child FPS–R, parent FPS–R
Position of Child During Injection						
Hallstrom,[17] 1968, US	Child position	Yes	N = 31; infants 6 wk to 6 mo; single center, university hospital clinic	NR	Mother holding infant (n = 15) or infant supine (n = 16); vaccine NR; lateral aspect of thigh	Cry
Ipp et al,[18†] 2004, Canada	Child position	Yes	N = 106; infants 2–6 mo; single center, primary care practice	Preterm birth; chronic disorder; prior hospitalization	Mother holding infant (n = 56) or infant supine (n = 50); DPTP, 0.5 mL IM; 25-gauge, 16-mm needle; anterolateral thigh	Observer Facial Grimace Scale, physician VAS, cry

(continued)

Table 1 (continued).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Kostandy,[19] 2005, US	Child position	Yes	N = 36; newborn infants on the 2nd day of life; single center, hospital maternity ward	Congenital anomalies; medical complications requiring oxygen/ventilatory support; mother a substance abuser	Mother holding diaper-clad neonate on chest (skin-to-skin) with blanket over top for 15 min before and 6 min after injection (n = 17) or infant clothed, supine, with blanket over top (n = 19); hepatitis B, IM; anterolateral thigh	Cry
Lacey et al,[20] 2008, US	Child position	Yes	N = 108; children 4–6 y; single center, hospital pediatric clinics	≥4 Surgeries/procedures within past 2 y; chronic illness; cognitive disability; physical impairment preventing sitting up	Sitting up (n = 53) or supine (n = 55); measles-mumps-rubella, DPTaP, and IPV	Child FPS, cry
Intramuscular vs Subcutaneous Injection						
Lafeber et al,[21] 2001, the Netherlands	Tissue site of injection	No	N = 67; infants 12–18 mo; setting NR	Allergy to vaccine components or egg; immune; coagulation disorder; previous vaccination or contraindication to vaccine; simultaneous injection of another vaccine	IM injection (n = 33) or SC injection (n = 34); measles-mumps-rubella; 0.5 mL; 0.5 × 19-mm needle; deltoid muscle	Parent Faces Pain Scale
Leung et al,[22] 1989, Canada	Tissue site of injection	No	N = 498; children 18 mo to 5 y; single center, ambulatory care clinic	Fever; intercurrent illness	IM injection with 25-gauge, 1-inch needle (n = 249) or SC injection with 27-gauge, 1/2-inch needle (n = 249); Hib; 0.5 mL; upper outer quadrant of buttock	Cry

(continued)

Table I (continued).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Mark et al,[2,3] 1999, Sweden	Tissue site of injection	No	N = 252; children 10 y; multicenter, school immunization clinics	Ongoing infection, hematologic disorder, or immunosuppressive condition	IM injection, 90° angle, 10 mm deep (n = 125) or SC injection, 30° angle, 5 mm deep (n = 127); DT; 0.25 mL; 25-mm needle; upper third of arm	Child VAS
Cooling the Skin at the Injection Site With Ice Before Injection						
Ebner,[24] 1996, US	Ice	No	N = 40; children 10–18 y; single center, hospital emergency room	Developmental disabilities; chronic illnesses; multiple trauma; urgent conditions; peripheral vascular disease; heart disease; Raynaud's phenomenon; cold; allergy; paroxysmal cold; hemoglobinuria; marked cold pressure response; cold sensitivity; non–English-speaking	Ice pack for 15 min (n = NR) or no ice (n = NR); tetanus	Child FPS
Gedaly-Duff and Burns,[25] 1992, US	Ice	No	N = 38; children 4–6 y; setting NR	NR	Ice cube in plastic bag on skin for 30 sec (n = 19) or no ice (n = 19); DPT (78%), DT (22%); 25-gauge, 5/8-inch needle (84%); deltoid (76%)	Child Oucher Scale, FPS, observer GMS

(continued)

Table I (continued).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Stroking the Skin Close to the Injection Site Before and During Injection						
Sparks,[26] 2001, US	Stroking the skin close to the injection site before and during injection	No	N = 105; children 4–6 y; multicenter, school clinics and walk-in public health clinic	NR	Stroking before and during injection (n = 35) or bubble blowing (n = 35) or control (n = 35); DPT (n = 22) or DTaP (n = 83); 0.5 mL IM; 22-gauge, 25-mm needle; vastus lateralis muscle	Child Oucher Scale
Order of Vaccine Injection When 2 Vaccines Were Administered Sequentially						
Ipp et al,[28] 2009, Canada	Order of vaccine injection	No	N = 120; infants 2–6 mo; single center, primary care practice	Acute febrile illness; chronic medical conditions; allergy to vaccine; concurrent use of topical anesthetics	DPTaP-Hib (Pentacel) first, then pneumococcus (Prevnar) (n = 60) or Prevnar first, then Pentacel (n = 60); 0.5 mL IM; 25-gauge, 22-mm needle; 90° angle; anterolateral thigh; 1–2 sec; alternate limbs for each injection	Observer MBPS, parent VAS, cry
Simultaneous vs Sequential Injection of 2 Vaccines						
Horn and McCarthy,[29] 1999, US	Simultaneous vs sequential injection	No	N = 46; children 4–6 y; single center, primary care practice	Mental or physical conditions; hospitalized within past 6 mo; injection within past 6 mo	Simultaneous injection (n = 24) or sequential injection (n = 22); DPT and measles-mumps-rubella	Child FPS, observer OSBD–R, parent VAS

(continued)

Table I (continued).

Author, Year, Country	Intervention Category	Included in Meta-Analysis	Population Enrolled, Setting	Exclusion Criteria	Intervention*	Outcomes
Vaccine Temperature						
Maiden et al,[30] 2003, Australia	Vaccine temperature	No	N = 150; children ≥16 y and adults; single center, hospital emergency room	Requiring inpatient treatment	No warming (n = 50) or rubbed 1 min between palms of hands (n = 50) or warmed 37°C for 5 min (n = 50); ADT; 0.5 mL IM; 23-gauge, 25-mm needle; 60° angle; deltoid	McGill Present Pain Intensity Questionnaire
Rapid Intramuscular Injection Without Aspiration						
Ipp et al,[31] 2007, Canada	Rapid injection without aspiration	No	N = 113; infants 4–6 mo; single center, primary care practice	Chronic illness; history of allergy to vaccine components; acute febrile illness; use of topical local anesthetic	Rapid injection without aspiration (~1 sec; n = 56) or slow injection with aspiration (~10 sec; n = 57); DPTaP-Hib; 0.5 mL IM; 25-gauge, 22-mm needle; 90° angle; anterolateral thigh	Observer MBPS, physician VAS, parent VAS, cry

MBPS = Modified Behavioral Pain Scale (range, 0–10); VAS = visual analog scale (range, 0–100 mm or 0–10 cm); NR = not reported; Oucher Scale (range, 0–100 or 0–5); CHEOPS = Children's Hospital of Eastern Ontario Pain Scale (range, 4–13); FPS-R = Faces Pain Scale–Revised (range, 0–100); DPTP = diphtheria, pertussis, tetanus, and polio; Facial Grimace Scale (range, 0–300); DPTaP = diptheria, polio, tetanus, acellular pertussis; IPV = inactivated polio virus; FPS = Faces Pain Scale (range, 0–100, 0–10, or 0–5); Parent Faces Pain Scale (constructed by the investigators for this study; range, 0–4); Hib = *Haemophilus influenzae* type b; DT = diphtheria-tetanus; DPT = diphtheria-pertussis-tetanus; GMS = Global Mood Scale (range, 1–7); DTaP = diphtheria, tetanus, and pertussis; DPTaP-Hib = diphtheria, polio, tetanus toxoid, acellular pertussis, inactivated polio, and *H influenzae* type b conjugate vaccine; OSBD-R = Observational Scale of Behavioral Distress–Revised (range, NR); ADT = adult diphtheria-tetanus; McGill Present Pain Intensity Questionnaire (range, 0–5).

*Trademarks: Priorix (SmithKline Beecham Pharma, Oakville, Ontario, Canada; and GlaxoSmithKline, Brentford, Middlesex, United Kingdom); M-M-R_{II} (Merck Frosst Canada & Co., Montreal, Quebec, Canada); Pluserix (no longer available commercially); RORVax (equivalent of M-M-R_{II}; Aventis Pasteur-MSD, Lyon, France); Pentacel (Sanofi Pasteur Ltd., Toronto, Ontario, Canada); Prevnar (Wyeth Pharmaceuticals, Inc., Montreal, Quebec, Canada).

†Prior participation occurred in <10% of enrolled cases.

Table II. Assessment of risk of bias of included trials (N = 19).

Author, Year, Country	Adequate Sequence Generation	Allocation Concealment	Blinding of Outcome Assessors and Patients	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
Different Formulations of the Same Vaccine							
Ipp et al,[12] 2004, Canada	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ipp et al,[13] 2006, Canada	Yes	Yes	Yes	Yes	Yes	Yes	Low
Knutsson et al,[14] 2006, Sweden	Yes	Yes	Yes	Yes	No	Unclear	High
Lyons and Howell,[15] 1991, Ireland	Yes	Yes	Yes	Yes	Yes	Yes	Low
Wood et al,[16] 2004, France	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Position of the Child During Injection							
Hallstrom,[17] 1968, US	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Ipp et al,[18] 2004, Canada	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Kostandy,[19] 2005, US	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Lacey et al,[20] 2008, US	Unclear	Unclear	No	Yes	Yes	Unclear	High
Intramuscular vs Subcutaneous Injection							
Lafeber et al,[21] 2001, the Netherlands	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Leung et al,[22] 1989, Canada	No	No	Unclear	Yes	No	Unclear	High
Mark et al,[23] 1999, Sweden	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Cooling the Skin at the Injection Site With Ice Before Injection							
Ebner,[24] 1996, US	Unclear	Unclear	No	Yes	No	Unclear	High
Gedaly-Duff and Burns,[25] 1992, US	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Stroking the Skin Close to the Injection Site Before and During Injection							
Sparks,[26] 2001, US	No	No	Unclear	Yes	Yes	Unclear	High

(continued)

Table II (continued).

Author, Year, Country	Adequate Sequence Generation	Allocation Concealment	Blinding of Outcome Assessors and Patients	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
Order of Vaccine Injection When 2 Vaccines Were Administered Sequentially							
Ipp et al,[28] 2009, Canada	Yes	Yes	Yes	Yes	Yes	Yes	Low
Simultaneous vs Sequential Injection of 2 Vaccines							
Horn and McCarthy,[29] 1999, US	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Vaccine Temperature							
Maiden et al,[30] 2003, Australia	Yes	Yes	Yes	Yes	Yes	Yes	Low
Rapid Intramusclar Injection Without Aspiration							
Ipp et al,[31] 2007, Canada	Yes	Yes	Yes	Yes	Yes	Yes	Low

CI, 0.30 to 0.52) and the RD was –0.27 (95% CI, –0.34 to –0.20). The NNT with Priorix to prevent 1 child from having pain was 3.7 (95% CI, 2.9 to 5.0).

The RR of crying could be determined for 3 trials reporting on the presence or absence of crying[12–14] in 404 infants and children. The incidence of crying was lower with Priorix than with M-M-R_{II} (RR, 0.66; 95% CI, 0.59 to 0.74; $P < 0.001$) (**Figure 2**).[12–14] Heterogeneity was not significant for this outcome. The RD was –0.31 (95% CI, –0.38 to –0.24; $P < 0.001$); and the NNT with Priorix to prevent 1 child from crying was 3.2 (95% CI, 2.6 to 4.2).

Data for parental VAS scores (range, 0–100 mm) could be combined for these 3 studies (VAS difference scores [injection phase minus baseline] in 2 studies[12,13] and parental VAS postvaccination scores in 1 study[14]). Priorix was associated with less pain (MD, –27.30 mm; 95% CI, –30.50 to –24.10; $P < 0.001$). Statistically significant heterogeneity was observed for this outcome ($\chi^2 = 8.19$; $P = 0.02$; $I^2 = 76\%$). The SMD was –1.5 (95% CI, –1.73 to –1.28; $P < 0.001$) with statistically significant heterogeneity ($\chi^2 = 23.67$; $P < 0.001$; $I^2 = 92\%$). Meta-analysis of postvaccination VAS scores for the 2 studies that included young children (unable to provide self-report)[12,14] revealed an MD of –29.10 mm (95% CI, –32.50 to –25.70; $P < 0.001$). Heterogeneity was not significant for this outcome. In the study that included children 4 to 6 years of age,[13] VAS difference scores were lower with Priorix than with M-M-R_{II} (MD, –13.50 mm; 95% CI, 23.60 to –3.40; $P = 0.009$).

In 2 trials[12,13] that included physician VAS difference scores (injection minus baseline; range, 0–100 mm) for 109 infants, the WMD was –20.50 mm (95% CI, –33.30 to –7.80; $P = 0.002$) for Priorix versus M-M-R_{II}. Heterogeneity was significant ($\chi^2 = 4.16$; $P = 0.04$; $I^2 = 76\%$). Individual analyses found a consistent pattern of results for each trial ($P < 0.05$ for both analyses; data NR). In 1 study,[12] MBPS difference scores were significantly lower for Priorix than for M-M-R_{II} (MD, –2.00; 95% CI, –3.70 to –0.32; $P = 0.02$).

In a study by Lyons and Howell,[15] which compared M-M-R_{II} and Pluserix, the risk of crying was lower with Pluserix (RR, 0.43; 95% CI, 0.22 to 0.86; $P = 0.02$; and RD, –0.28; 95% CI, –0.49 to –0.08; $P = 0.006$). The NNT to prevent 1 infant from crying was 3.6 (95% CI, 2.0 to 12.5).

Position of the Child During Injection

Four studies[17–20] investigated the effect of child positioning on pain response during vaccine injection in 281 infants and children (**Table I**). Three of the studies[17–19] investigated the effect of holding infants (vs lying supine) during vaccine injection, and 1 study[20] investigated the effect of sitting up (vs lying supine) in children 4 to 6 years of age. In the trial by Lacey et al,[20] pain was measured in children after 3 vaccines were injected. The risk of bias was unclear for 3 of the studies[17–19] and high for 1 study[20] (**Table II**).

Data on the duration of crying were combined from the 4 studies including 281 children.[17–20] The SMD was –0.22 (95% CI, –0.46 to 0.02; $P = 0.07$) (**Figure 3**). Significant heterogeneity was observed for this outcome ($\chi^2 = 8.51$; $P = 0.04$; $I^2 = 65\%$).[17–20] A separate meta-analysis for the 3 studies in preverbal children[17–19] also revealed significant heterogeneity ($\chi^2 = 8.36$; $P = 0.02$; $I^2 = 76\%$); the data were thus analyzed qualitatively.

Three studies[17,19,20] reported greater pain scores for children assigned to the supine position during immunization. In the study by Kostandy,[19] holding newborn infants (skin-to-skin contact, or *kangaroo care*) resulted in a significant reduction in the duration of crying in the first minute after injection (MD, –8.20 sec; 95% CI, –15.32 to –1.08; $P = 0.02$). The SMD for this outcome was –0.74 (95% CI, –1.42 to –0.06; $P = 0.03$). In the study by Hallstrom,[17] infant crying (scored as the AUC of cry duration and intensity by a sound-level meter) in the first 10 seconds after vaccine injection was lower for infants being held by mothers than for infants lying supine (MD, –13.90; 95% CI, –25.80 to –2.00; $P = 0.02$). The SMD for this outcome was –0.80 (95% CI, –1.54 to –0.07; $P = 0.03$). In the study by Lacey et al,[20] the child-reported FPS score (range, 0–10) was lower when the child was sitting up (MD, –1.00; 95% CI, –1.94 to –0.06; $P = 0.04$). The SMD for this outcome was –0.40 (95% CI, –0.78 to –0.02; $P = 0.04$). The duration of crying was shorter when the child was sitting up (or being held), but the difference was not statistically significant. Likewise, Ipp et al[18] found no significant effect of holding infants, as assessed using facial grimacing and physician VAS scores.

Intramuscular Versus Subcutaneous Injection

Three studies[21–23] compared injection pain for vaccines administered intramuscularly and subcutaneously (**Table I**). Quality assessments revealed an un-

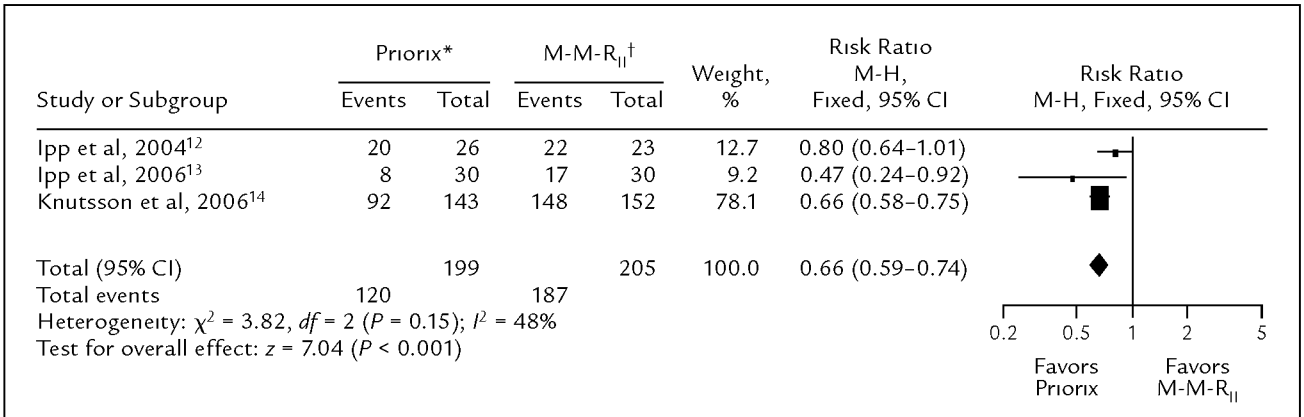

Figure 2. Effect of formulation of measles-mumps-rubella vaccine on incidence of crying during vaccine injection. M-H = Mantel-Haenszel; *df* = degrees of freedom. *Trademark: Priorix (SmithKline Beecham Pharma, Oakville, Ontario, Canada and GlaxoSmithKline, Brentford, Middlesex, United Kingdom; †Trademark: M-M-R_{II} (Merck Frosst Canada & Co., Montreal, Quebec, Canada).

clear risk of bias for 2 studies[21,23] and a high risk of bias for the other study[22] (**Table II**).

Data were not combined for any of the included trials. In the study by Mark et al,[23] using child self-reported pain, no significant difference was found between intramuscular and subcutaneous injections with respect to the proportion of children reporting any pain or child VAS pain score. The study by Leung et al[22] reported an increase in pain following intramuscular injection, based on the presence of crying (RR, 1.72; 95% CI, 1.37 to 2.17; $P < 0.001$), whereas the study by Lafeber et al[21] reported no significant difference between intramuscular and subcutaneous injections, based on Parent Faces Pain Scale scores.

Cooling the Skin at the Injection Site With Ice Before Injection

Two trials[24,25] studied the effects of cooling the skin at the injection site with ice before vaccine injection (**Table I**). The quality assessment indicated an

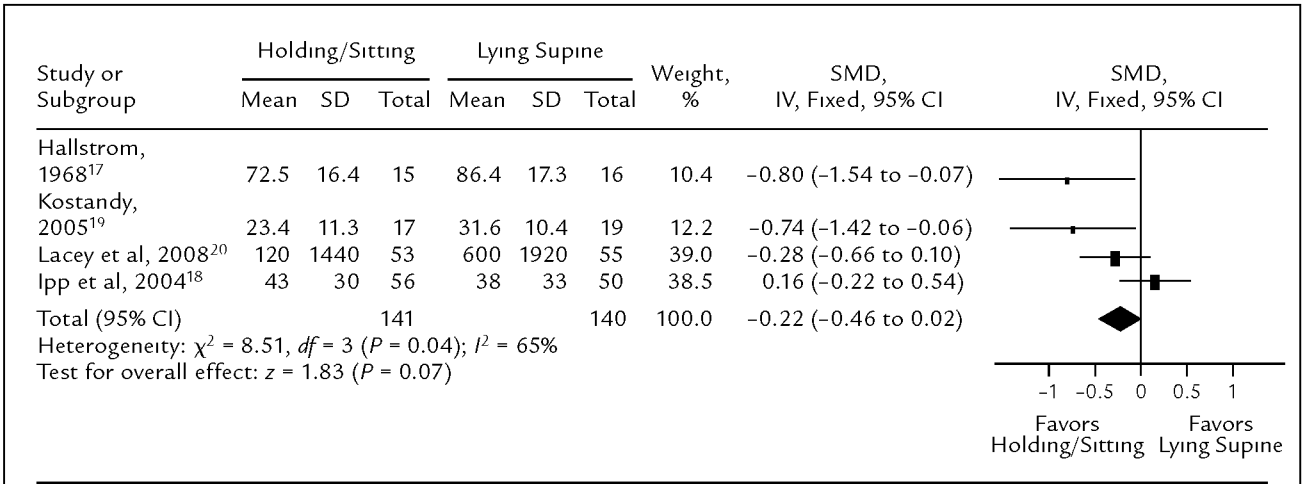

Figure 3. Effect of position of child on cry duration during vaccine injection. SMD = standardized mean difference; *df* = degrees of freedom.

unclear risk of bias for 1 study[25] and a high risk of bias for the other study[24] (Table II).

In the study by Gedaly-Duff and Burns,[25] pain response did not differ significantly between children who received ice and those who received no ice, as assessed by the children themselves using the Oucher Scale or the FPS. Similarly, nurse reports of child intensity and distress using the Global Mood Scale[32] did not differ significantly between the groups. In the second study, by Ebner,[24] no statistically significant differences were observed between the groups for child self-reported pain using the FPS; however, summary statistics were not provided.

Stroking the Skin Close to the Injection Site Before and During Injection

A study by Sparks[26] explored the effects of cutaneous stimulation (Table I). Cutaneous stimulation was delivered by stroking the skin close to the injection site with moderate intensity and in a rhythmic fashion before and during the injection. The quality rating indicated a high risk of bias (Table II). Child self-reported pain in this study (n = 66) using the Oucher Scale (range, 0–5)[4] revealed less pain for children who received stroking than for those who received no stroking (MD, –1.00; 95% CI, –1.90 to –0.10; $P = 0.03$). The SMD for this outcome was –0.53 (95% CI, –1.02 to –0.04; $P = 0.03$).

Order of Vaccine Injection When 2 Vaccines Were Administered Sequentially

One study by Ipp et al[28] examined whether pain differed for 2 distinct vaccines according to the order in which they were administered to 120 infants. In that study, diphtheria-polio-tetanus-acellular pertussis-*Haemophilus influenzae* type b (DPTaP-Hib§) and pneumococcal conjugate vaccine (PCV‖) were given sequentially; the order of their administration was randomized (Table I). Pain was assessed after each injection and overall. The study quality rating indicated a low risk of bias (Table II).

When administered first, DPTaP-Hib was less painful than PCV, as assessed by observer MBPS ratings (range, 0–10)[6] (MD, –1.90; 95% CI, –2.69 to –1.11; $P < 0.001$), parent VAS scores (range, 0–100 mm) (MD, –28.00 mm; 95% CI, –37.50 to –18.50; $P < 0.001$), and the presence of crying (RR, 0.71; 95% CI, 0.59 to 0.85; $P < 0.001$; and RD, –0.28; 95% CI, –0.41 to –0.16; $P < 0.001$). The NNT to prevent 1 infant from crying was 3.6 (95% CI, 2.4 to 6.3).

During the second injection, pain was lower when DPTaP-Hib was given first (and PCV second) than when the vaccines were given in the reverse order, for observer MBPS scores (MD, –0.80; 95% CI, –1.33 to –0.27; $P = 0.003$), but not for parent VAS scores. Fewer infants cried during the second injection when DPTaP-Hib was given first, but the difference was not statistically significant.

Overall pain from both vaccine injections was significantly lower in infants who received DPTaP-Hib first, as assessed by observer MBPS ratings (MD, –0.60; 95% CI, –1.14 to –0.06; $P = 0.03$) and parent VAS scores (MD, –14.00 mm; 95% CI, –22.80 to –5.20; $P = 0.002$). The SMDs for these outcomes were –0.40 (95% CI, –0.76 to –0.04; $P = 0.03$) and –0.57 (95% CI, –0.93 to –0.20; $P = 0.002$), respectively.

Simultaneous Versus Sequential Injection of 2 Vaccines

One study by Horn and McCarthy[29] determined the effect of simultaneous versus sequential injection of 2 separate vaccines (Table I). The quality assessment for this study indicated an unclear risk of bias (Table II).

In that study,[29] no significant differences in child self-reported distress, using the FPS (range, 0–5), parent VAS difference scores (injection minus baseline; range, 0–100 mm), and OSBD–R (range, NR), were observed between simultaneous and sequential injections.

Vaccine Temperature

A study by Maiden et al[30] conducted in children and adults ≥16 years of age investigated the effect of warming the vaccine before injection (Table I). The quality assessment indicated a low risk of bias (Table II). For the entire study sample, investigators reported no significant differences among the 3 treatment arms (cold, rubbed, or warmed vaccine). The number (%) of participants with pain in each group was 15 (30%), 19 (38%), and 15 (30%), respectively. Self-reported pain scores, however, were not provided for the children who participated; thus, the effectiveness of this intervention could not be determined.

§Trademark: Pentacel (Sanofi Pasteur Ltd., Toronto, Ontario, Canada).

‖Trademark: Prevnar (Wyeth Pharmaceuticals, Inc., Montreal, Quebec, Canada).

Rapid Injection Without Aspiration for Intramuscular Injection

A study by Ipp et al[31] compared the pain that occurred during intramuscular vaccine injection in 113 infants using 2 techniques: rapid injection without aspiration and slow injection with aspiration (**Table I**). The quality rating for the trial indicated a low risk of bias (**Table II**). The median (interquartile range) duration of vaccine injection was 0.9 second (range, 0.8–1.1) for the group that received rapid injection without aspiration and 8.8 seconds (range, 7.9–10.3) for the group that received slow injection with aspiration ($P < 0.001$).

Rapid injection without aspiration was less painful, as assessed using observer MBPS scores (range, 0–10) (MD, –2.30; 95% CI, –3.17 to –1.43; $P < 0.001$); cry duration (MD, –14.70 sec; 95% CI, –20.32 to –9.08; $P < 0.001$); parent VAS difference scores (range, 0–100 mm) (MD, –16.00 mm; 95% CI, –25.50 to –6.50; $P < 0.001$), and physician VAS difference scores (range, 0–100 mm) (MD, –14.00 mm; 95% CI, –21.30 to –6.70; $P < 0.001$). The SMDs were –0.97 (95% CI, –1.36 to –0.58; $P < 0.001$); –0.95 (95% CI, –1.34 to –0.56; $P < 0.001$); –0.62 (95% CI, –0.99 to –0.24; $P = 0.001$); and –0.70 (95% CI, –1.08 to –0.32; $P = 0.003$), respectively.

In addition, fewer infants cried (RR, 0.52; 95% CI, 0.38 to 0.72; $P = 0.001$; and RD, –0.40; 95% CI, –0.56 to –0.23; $P < 0.001$). The NNT to prevent 1 infant from crying was 2.5 (95% CI, 1.8 to 4.3).

DISCUSSION

We found that certain physical interventions and injection techniques can be used by vaccinators to reduce the pain experienced by children during vaccine injection, whereas others cannot be recommended for that purpose (**Table III**). In terms of using different formulations of the same vaccine, the finding that

Table III. Effectiveness of the physical and operator-dependent techniques assessed in the systematic review.

Intervention*	Reduced Pain*
Different formulations of the same vaccine (eg, different brands of measles-mumps-rubella vaccine)	Yes
Upright positioning of children (and holding infants) during injection	Yes
Stroking the skin close to the injection site before and during injection	Yes
Order of vaccine injection when 2 injections are administered sequentially	Yes
Combined injection technique: rapid injection without aspiration for intramuscular injection	Yes
Intramuscular rather than subcutaneous injection	?
Cooling the skin at the injection site with ice before injection	?
Simultaneous rather than sequential injection of 2 vaccines	?
Warming the vaccine	?
Injection into different anatomic locations (arm, leg, or buttock)	NA
Aspects of needle (gauge, length, angle of insertion, and speed of injection)	NA

Yes = there is evidence to support the stated intervention; ? = there is insufficient evidence to support the stated intervention; NA = not applicable (none of the trials assessed the stated intervention).
*See text for details.

the M-M-R_{II} vaccine is more painful than either Priorix or Pluserix was consistent among the RCTs in this review,[12–16] and quality assessments for 3 of the 5 relevant RCTs revealed a low risk of bias. In addition, studies evaluated pain in children of different ages, increasing the generalizability of the findings. The SMDs revealed values of ≥0.66 for included outcomes, reflecting a moderate to large intervention effect.[10] The magnitude of pain reduction conferred by Priorix ranged from ~15 to 30 mm on a 100-mm scale, and the NNT to prevent 1 child from crying was 3.2. The finding that diverse brands of the same vaccine were observed to cause different levels of pain is not surprising given that the properties of these formulations differ, notably the pH, which can affect pain perception. In another study,[26] less pain was reported for children who received the acellular diphtheria-tetanus-pertussis vaccine than for those who received the whole cell vaccine, with deviation from physiologic pH cited as the possible explanation; however, the difference was not statistically significant. Taken together, there is evidence for using Priorix instead of M-M-R_{II} to reduce the pain associated with vaccine injection.

Sufficient evidence was found to suggest a reduced pain response as a function of body position during immunization. A meta-analysis of 4 included studies[17–20] indicated a standardized effect size of –0.22 ($P = 0.07$); however, significant heterogeneity led to qualitative analyses of the individual studies. Upright positioning (for school-aged children) or maternal holding (for infants) was associated with reduced pain when compared with children lying down in 3 of the studies[17,19,20]; the SMD ranged from 0.40 to 0.84 in the individual studies, indicating a moderate to large effect size.[10] The quality scores of the 4 studies indicated an unclear risk of bias for 3 studies[17–19] and a high risk of bias for the remaining study.[20] The observed benefits are consistent with a study of immunization pain in infants conducted by Santoro and Grandone,[34] which was excluded from the review because it was published as a research letter. In addition, results of the study by Kostandy,[19] which found that newborn infants who were undressed (except for a diaper) and were held by their mothers against their chests (an approach referred to as *kangaroo care*) experienced less pain than infants in the supine position, are consistent with results of other studies in preterm and full-term newborn infants undergoing other needle puncture procedures.[35–38]

In the only study that did not find a benefit of infant holding,[18] methodologic heterogeneity may explain the results. In that study, mothers could pick up infants in the control group (lying supine) at any time after injection, and mothers may have preferentially picked up infants that were more distressed, negating the benefits of holding. This explanation is supported by the study by Hallstrom,[17] which found that differences between the infants who were held and those who were supine did not persist after mothers of infants in the supine group had picked them up. Taken together, these data support keeping children in an upright position (or parental holding of infants) to reduce pain and distress during vaccine injections.

It has been hypothesized that children feel less fear when sitting up than when lying down.[20] Parents also prefer to have their children sitting up for injections, and the upright position does not increase the duration of the procedure.[20] Sitting up has been recommended for children as soon as they can maintain head and trunk control (ie, 3–5 months of age), accompanied by parental holding for added support and comfort.[39,40] Immobilization of children during procedures (eg, holding children's legs or arms), although not specifically reviewed in this study, is worthy of comment. Immobilization may heighten distress in children.[41] Children struggle to move when they are restrained, and restraint can lead to psychological trauma.[42] Methods of positioning children that support the child, and effectively expose and secure limbs during vaccine injection without undue force are therefore also recommended.

There was insufficient evidence to support a difference in pain based on the route of vaccine administration (intramuscular vs subcutaneous).[21–23] This may be due to: lack of a difference (ie, equivalence) between routes; differences that are too small to be detected reliably; or variability in pain that depends on the attributes (ie, painfulness) of the vaccine or sensitivity of the tool being used to measure pain. It is important to note that the quality ratings revealed an unclear risk of bias for 2 of the studies[21,23] and a high risk of bias for the remaining study.[22] Methodologic variability in the injection technique may also explain the results. In the only study that reported more pain after intramuscular injection than after subcutaneous injection,[22] it was unclear whether intramuscular injections were performed using aspiration, a technique that increases pain.[31] Moreover, there was variability in the body region that was injected (deltoid and but-

tock), and it is currently undetermined whether pain varies according to the region being injected.

A recent overview of the evidence base supporting current guidelines for the route of administration of vaccines has revealed a lack of attention to this issue in vaccine trials.[43] At present, all vaccines containing aluminum as the adjuvant are recommended for intramuscular injection (with the exception of anthrax vaccine) because of a lower incidence of adverse effects at the injection site.[43] Live attenuated virus vaccines, on the other hand, are traditionally administered subcutaneously. Currently, there is no consensus about the optimal route of administration of nonadjuvant subunit and whole cell vaccines. In studies that have compared intramuscular and subcutaneous administration of the same vaccine, intramuscular injection has led to a similar, if not better, immunogenicity and injection site tolerability profile.[43] Future research is needed to further investigate the effect of route of administration on pain during vaccine injection. This includes investigation of the pain from intradermal injection, for which no studies were identified in the present review. Intradermal injection has been suggested as an alternate method of vaccine administration to reduce the total dose (and volume) of antigen used.[44]

Insufficient evidence was found to support the use of ice on the skin before immunization as a pain-reducing strategy. This result, however, was limited to data from 2 studies.[24,25] The quality ratings revealed an unclear risk of bias for 1 of the studies[25] and a high risk of bias for the other study.[24] It is possible that the lack of effect observed in these studies may reflect deficiencies in study methodology, including inappropriate duration of ice application (either too short or too long). In addition, the analgesia produced by ice may be too mild to be important clinically. Because of the presence of potential confounders in the relevant studies (eg, the need for additional painful procedures, concomitant interventions by nonblinded personnel), no definitive conclusions could be drawn. In contrast, pain-relieving effects of ice have been reported in adults undergoing injections.[45,46]

In addition to the ineffectiveness of ice as an analgesic intervention in children undergoing immunization, there may be specific contraindications to using ice in young children because they lack the cognitive maturity to understand the role of ice. In this population, ice can even lead to a paradoxical effect (ie, increase rather than decrease pain). This is because children may perceive the cold sensation as painful, which contributes to overall pain perception. In addition, ice can focus the child's attention on the injection site and thus the pain caused by the procedure. In summary, ice cannot be recommended for reducing pain during vaccine injection in children. Additional research is recommended, but only in selected age groups, including school-aged children and adolescents. The reader is referred to the article by Shah et al[47] in this supplement for a summary of the effectiveness of vapocoolant (refrigerent) sprays. These chemical sprays are an alternative method of cooling the skin for the purpose of reducing the pain from needle punctures.

Stroking the skin close to the injection site before and during vaccine injection was found to reduce pain.[26] The SMD for this intervention was 0.53, indicating a moderate effect size.[10] The magnitude of the effect was 1 point on the Oucher Scale (range, 0–5). These findings, however, were based on a single study[26] with a high risk of bias, and children were simultaneously told by the vaccinator to "keep thinking about how nice that feels." Further studies are needed to confirm the findings. It is important to note, however, that using hands to touch or massage areas of the body that are painful is the oldest, most universally recognized way of responding to pain.[48] Stroking the limb has been found to reduce pain in preterm infants undergoing heel lance procedures.[49] In addition, pressure applied to the site before injection has been found to reduce pain in adults undergoing intramuscular vaccine and immune globulin injections.[48,50] The benefit of touch on reducing pain perception is hypothesized to be the result of activation of large-diameter (touch) neurons that compete with small-diameter (pain) neurons activated during painful procedures, resulting in reduced nociceptive input transmission to the brain.[51]

It is important to distinguish between stroking or rubbing the skin proximal to the injection site before and during injection and rubbing the injection site after injection. Rubbing the injection site after injection may increase the risk of delayed local reactions.[52] Taken together, these data suggest that stroking the skin close to the injection site reduces pain during vaccine injection.

We found that when 2 distinct vaccines were injected sequentially, injection of the least painful vaccine first not only reduced pain from the first injection but also reduced overall pain from both injections.

The SMD for this intervention was –0.40 to –0.57, indicating a moderate effect size.[10] This effect size was equivalent to a reduction of 14 mm on the 100-mm VAS or 0.6 point on the 10-point MBPS scale. This finding is based on a single high-quality RCT.[28] The findings are consistent with animal and human studies, which found a relationship between future pain and previous pain, and increasing pain following repeated noxious sensory stimulation.[53–57] Taken together, there is sufficient evidence to support injection of the most painful vaccine last to reduce pain when 2 vaccines are to be given during the same office visit. It is reasonable to apply the same principle to situations when >2 injections are to be given.

We found insufficient evidence to support the practice of injecting 2 vaccines simultaneously rather than sequentially to reduce pain. This conclusion was based on the results of a single trial[29] that was conducted in children 4 to 6 years of age, and the quality rating for that study revealed an unclear risk of bias; therefore, no definitive conclusions could be drawn. Moreover, no attempt was made to standardize the order of administration of the vaccines (diphtheria-pertussis-tetanus and measles-mumps-rubella) in the group of children randomized to sequential injections, even though order of injection may impact the overall pain experience.[28] Despite these limitations, the results are consistent with those of a separate study conducted in 9- to 12-month-old infants, which was published as an abstract.[58] Additional research comparing the impact of simultaneous and sequential vaccine injections appears warranted.

In the only included study of simultaneous versus sequential vaccine injection,[29] 96% of the parents whose children participated in the simultaneous injection group preferred simultaneous injections, whereas only 50% of the parents whose children participated in the sequential injection group preferred sequential injections. This observation is noteworthy because it suggests that, even in the absence of a difference in vaccine injection pain, parents (and potentially children and health care workers) may still have preferences for certain injection techniques over others. Preferences should be accommodated whenever possible, because they can affect overall consumer and health care worker satisfaction with the immunization process. In particular, it would be important to investigate the child's preferences.

There was insufficient evidence of a benefit of warming the vaccine on pain response during injection. This finding was based on a study[30] with a low risk of bias. However, the study included children (≥16 years of age) and adults (≥18 years of age), and the pain scores for the children who participated could not be separated from the scores for adults. It is possible that the lack of a difference among treatment conditions (ie, cold, rubbed, or warmed) was due to a long delay between vaccine preparation and injection, such that the resultant vaccine temperatures at the time of injection (ie, 19°C, 27°C, and 29°C, respectively) were too close to detect a difference. Alternatively, it is possible that the effects depend on the inherent painfulness of the vaccine being administered. Studies of adults undergoing injection of local anesthetics reported less pain when the solutions were warmed than when the solutions were kept at room temperature.[59] Conversely, no difference in pain has been observed in adults undergoing immunization with needles of different temperatures (cold vs room temperature).[60]

It is also important to consider the effect of warming vaccines on their biologic activity. Vaccines are sensitive biologic products that may become less effective, even destroyed, when exposed to temperatures outside the recommended range. Correct storage and handling of vaccines are, therefore, of paramount importance. "Cold chain" refers to the process used to maintain optimal conditions during the transport, storage, and handling of vaccines, starting at the manufacturer and ending with the administration of the vaccine to the patient. The optimum temperature for refrigerated vaccines is 2° to 8°C. For frozen vaccines, the optimum temperature is –15°C or lower. In addition, protection from light is a necessary condition for some vaccines.[61] The effect of warming vaccines before administration has the potential to interfere with effectiveness and should not be undertaken without first investigating the potential effect on vaccine effectiveness. Based on the lack of proven analgesic effect and potential of altering vaccine effectiveness, changing the temperature of the vaccine is not recommended.

Evidence to support the use of rapid intramuscular injection without aspiration for reducing pain during vaccine injection is based on the results of a single high-quality RCT.[31] The SMDs ranged from –0.62 to –0.97 for measured pain outcomes, indicating a moderate to large effect size.[10] For cry duration, the mean reduction was 15 seconds, and the NNT to prevent 1 child from crying was 2.5. The relative contri-

bution of aspiration versus injection speed could not be determined in this study, and the possible impact of each component on pain perception is summarized here.

The process of aspiration, which involves pulling back on the plunger (applying negative pressure on the syringe) after needle puncture has occurred, has been recommended as a safety measure to ensure that a blood vessel has not been penetrated, but has never been studied in a scientific manner. In addition to increasing the duration of the procedure, this extra step is often associated with unintentional displacement (ie, movement) of the needle within the tissue, leading to more pain, when compared with no aspiration. In clinical practice, aspiration may not be necessary because there is little risk of penetrating major blood vessels in any of the locations routinely used for vaccine injection.[62] Moreover, aspiration does not accomplish the safety objective for which it was designed because most vaccinators perform the procedure too quickly for it to be effective.[63] Effective aspiration may require 5 to 10 seconds,[64] substantially longer than most vaccinators take to inject vaccines. Approximately one third of vaccinators do not aspirate before vaccine injection,[1] and there are no published reports of adverse effects associated with this practice. In addition, bleeding at the injection site is common[62] and does not signal incorrect injection technique. Recent vaccine injection recommendations from the Public Health Agency of Canada[65] indicate that aspiration before injection is optional. Based on the data from this review, we recommend that aspiration before intramuscular injection of vaccines be avoided to reduce injection pain.

With respect to injection speed, "injecting slowly" has been a basic tenet of injecting medications. The rationale for this practice is that slow injection minimizes pressure and sudden distention of tissues. The definition of a slow injection, however, is unclear. Some researchers have quantified *slow* to mean between 5 and 10 sec/mL.[66] In clinical practice, actual injection speeds have been observed to be faster. In fact, the slowest observed speed was closer to 4 sec/mL.[66] The duration of injection for each condition in the study by Ipp et al[31] was not specified. Based on the information provided in the Methods section of the paper, it could have varied from as fast as 2 sec/mL for a rapid injection without aspiration to 10 sec/mL for a slow injection with aspiration. It is not clear whether a difference of 8 sec/mL is sufficient to affect pain response.[67] In adults, no consistent pattern of effect has been observed when injection speeds of 5 to 10 sec/mL were compared with a speed of 30 sec/mL or when 1 sec/mL was compared with 10 sec/mL.[66–68] Based on the available evidence, we recommend that vaccinators use rapid injection without aspiration, as described in the study by Ipp et al,[31] for intramuscular vaccine injection. The specific effect of injection speed requires further study.

None of the studies identified in our literature search evaluated the specific effects of the anatomic location of vaccine injection (arm, leg, or buttock) or needle characteristics (gauge, length, angle of insertion, or speed of injection). Studies of the mechanics of injection motion suggest that a linear motion of the needle (rather than a curved, nonlinear injection path) is required to minimize pain.[69] Further investigation of the possible effects of such factors on acute vaccine injection pain in children is warranted.

Finally, we could not compare the effectiveness of a single physical intervention and/or injection technique with that of combined strategies. Trials may have used multiple strategies simultaneously, but only assessed the impact of one. For instance, in the study by Ipp et al,[28] which evaluated the impact of varying the order of vaccine injection when 2 different vaccines were administered sequentially, the investigators administered other pain-relieving strategies (ie, rapid injection without aspiration, infant holding during the injection) equally to both study groups. The incremental benefit of each intervention is not known. However, in a separate systematic review in this supplement, conducted by Shah et al,[47] the investigators reported improved analgesia from combined interventions from different domains (eg, physical, psychological, and pharmacologic). It is reasonable to conclude that utilization of multiple pain-reducing physical and injection techniques will lead to improved analgesia when compared with single interventions.

Limitations of this review included: small number of studies, small number of children, limited number of vaccines, low quality ratings, publication bias, variability in pain assessment, and missing summary statistics (for a few trials). Considering the vast number of vaccine injections that are performed per year worldwide, it is surprising that such little empiric evaluation of pain-relieving injection interventions has been undertaken. We developed a broad search

strategy to maximize the number of studies that could be included. We screened a substantial number of studies but only identified 19 trials that were eligible for inclusion. It is possible that some trials were missed; however, this risk was reduced by having 2 reviewers screen the selected articles and by retrieving articles from reference lists in the selected articles.

In addition, the included studies often involved a relatively small number of children or children of a limited age range, and only a small number of vaccines were evaluated, making extrapolation to other ages and/or vaccines potentially problematic. The risk of bias was high or unclear for 68.4% (13/19) of the included trials, leading to uncertainty of the internal validity of the findings. It should be noted, however, that many trials were published before the CONSORT (Consolidated Standards of Reporting Trials) guidelines[70] were adopted, and the more recently published trials had higher quality assessments. Furthermore, word-count restrictions for manuscripts may have caused methodologic details to be excluded from some studies. There was a potential for publication bias based on selective publishing of studies with positive results. We attempted to minimize publication bias by including all identified reports, including theses. We also included studies published in any language. Studies used various methods of assessing pain in children, which made it difficult to combine and contrast the results. To address this issue, data were analyzed using SMDs in addition to WMDs. The authors of 1 study[24] could not be contacted for missing data, preventing a meta-analysis from being performed for the effect of ice; it is possible that the interpretation of the benefits of this intervention was affected.

This review did not address adverse reactions to vaccines that occur in the hours to days that follow vaccine injection, including pain. Some evidence suggests that postimmunization adverse effects are also affected by aspects of the injection, the tissue that is injected, and the anatomic location of the injection.[71–74] A separate review addressing these issues has recently been published.[75]

Evidence-based practice is recognized as a requirement in current health care environments. However, it is not the norm for many aspects of health care, including immunization pain management.[2] One of the most important barriers to adequate pain management is lack of knowledge about effective strategies.[2] Relatively little research has been undertaken to determine how to effectively disseminate research evidence into this practice area. Development of practice guidelines is 1 strategy for translating research evidence into a concrete, easily understandable proposal for change. The mere presence of practice guidelines, however, does not ensure that clinicians and patients will follow them.[76] Educational efforts are required for vaccinators and parents to ensure that they are equipped with the knowledge needed to provide adequate pain relief for children during immunization.

Acute pain from vaccine injections will soon be incorporated as an outcome in vaccine trials.[77] Vaccine manufacturers and government agencies are encouraged to investigate and supply vaccines and injection systems that are the least painful to children. In addition, new technologies that decrease pain warrant further research. These include adjustment of physicochemical characteristics of new vaccines to be less painful and use of combination vaccines, microneedles, and needle-free (eg, oral, transdermal, mucosal, inhalational) approaches.

CONCLUSIONS

Vaccinators can reduce pain in children undergoing vaccine injection by: administering brands of vaccines that are less painful, positioning children upright (and holding infants), stroking the skin close to the injection site before and during injection, administering the least painful vaccine first when 2 vaccines are to be injected sequentially during a single office visit, and performing intramuscular injections rapidly, without aspiration.

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Appendix. Search strategies for MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials.

Set	History	Results	Comments
MEDLINE Search Strategy (1950–October, Week 3, 2008)			
1	Pain Measurement/ or exp pain/ or Antibody Formation/ or Crying/ or anxiety/ or fear/ or panic/ or (adverse adj2 effect:).ti,ab. or (side adj2 effect:).ti,ab. or (skin adj2 reaction:).ti,ab. or (distress* or discomfort* or fright* or anxious).ti,ab.	602,135	Pain terms
2	Back/ or lumbosacral region/ or sacrococcygeal region/ or upper extremity/ or arm/ or muscle, skeletal/ or quadriceps muscle/ or (deltoid or thigh).ti,ab. or immunization/ or immunization, passive/ or adoptive transfer/ or immunotherapy, adoptive/ or immunization schedule/ or immunization, secondary/ or immunotherapy, active/ or vaccination/ or mass immunization/ or (simultaneous or sequential).ti,ab.	405,812	Immunization or vaccine terms
3	Needles/ or (needle: adj2 (gauge: or length: or thick: or angle: or size:)).ti,ab. or injections/ or injections, intramuscular/ or injections, subcutaneous/ or injections, intradermal/ or injections, jet/ or biolistics/ or ((needle: or inject: or vaccinat:) adj2 (technique: or technic: or aspirat: or angle: or speed: or slow: or rapid: or order:)).ti,ab. or massage:.mp. or (pressure or cuddling or cuddle: or hold: or ices or ice or iced or cold or hot or temperature).ti,ab. or (freezing or freeze or freezes).ti,ab. or refrigeration/ or (shot adj2 blocker).ti,ab. or exp vaccines/	1,015,481	Needle type or injections terms
4	Guidelines as topic/ or practice guidelines as topic/ or evaluation studies as topic/ or exp clinical trials as topic/ or validation studies as topic/ or ((clinical: adj5 trial:) or random: or ((singl: or doubl: or tripl: or trebl:) adj5 (mask: or blind:)) or (control: adj5 group:) or (quasi adj5 randomiz:) or (quasi adj5 randomis:)).ti,ab. or (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or validation studies).pt.	1,445,589	Study design/ methodology terms
5	1 and 2 and 3 and 4	1658	Base clinical set
6	Limit 5 to humans	1507	Human limit
7	Limit 6 to "all child (0 to 18 years)"	575	Age group limit
8	6 and (neonat: or newborn: or infan: or child: or adolescen: or teen:).mp.	598	Age group textwords
9	8 or 7	580	Final results

(continued)

Appendix (continued).

Set	History	Results	Comments
EMBASE Search Strategy (1980–2008, Week 43)			
1	Pain assessment/ or pain/ or injection pain/ or vaccination reaction/ or exp application site reaction/ or exp injection site reaction/ or antibody production/ or crying/ or facial expression/ or gesture/ or fear/ or anticipatory anxiety/ or anxiety/ or (adverse adj2 effect:).ti,ab. or (side adj2 effect:).ti,ab. or (skin adj2 reaction:).ti,ab. or (distress* or discomfort* or fright* or anxious).ti,ab.	408,946	Pain terms
2	Back/ or arm muscle/ or back muscle/ or deltoid muscle/ or quadriceps femoris muscle/ or lumbosacral spine/ or exp arm/ or exp leg/ or immunization/ or mass immunization/ or passive immunization/ or active immunization/ or immunotherapy/ or adoptive immunotherapy/ or adoptive transfer/ or vaccination/ or bcg vaccination/ or influenza vaccination/ or measles vaccination/ or revaccination/ or (simultaneous or sequential).ti,ab.	359,015	Immunization or vaccine terms
3	Needle/ or exp Injection/ or intradermal drug administration/ or intramuscular drug administration/ or intraosseous drug administration/ or subcutaneous drug administration/ or transdermal drug administration/ or (needle: adj2 (gauge: or length: or thick: or angle: or size:)).ti,ab. or injections/ or injections, intramuscular/ or injections, subcutaneous/ or injections, intradermal/ or injections, jet/ or biolistics/ or ((needle: or inject: or vaccinat:) adj2 (technique: or technic: or aspirat: or angle: or speed: or slow: or rapid: or order:)).ti,ab. or massage:.mp. or (pressure or cuddling or cuddle: or hold: or ices or ice or iced or cold or hot or temperature).ti,ab. or (freezing or freeze or freezes).ti,ab. or refrigeration/ or (shot adj2 blocker).ti,ab. or exp *Vaccine/	883,327	Needle type or injections terms
4	Exp clinical trial/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or validation study/ or (evaluation studies or evaluation study).ti,ab. or exp practice guideline/ or ((clinical: adj5 trial:) or random: or ((singl: or doubl: or tripl: or trebl:) adj5 (mask: or blind:)) or (control: adj5 group:) or (quasi adj5 randomiz:) or (quasi adj5 randomis:)).ti,ab.	1,086,821	Study design/ methodology terms
5	1 and 2 and 3 and 4	2599	Base clinical set
6	Limit 5 to humans	2452	Human limit

(continued)

Appendix (continued).

Set	History	Results	Comments
7	Limit 6 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	609	Age group limit
8	6 and (neonat: or newborn: or infan: or child: or adolescen: or teen:).mp.	833	Age group textwords
9	7 or 8	827	Final results
CINAHL Search Strategy (1982–October, Week 4, 2008)			
1	Treatment related pain/ or pain measurement/ or exp pain/ or antibody formation/ or crying/ or anxiety/ or fear/ or (adverse adj2 effect:).ti,ab. or (side adj2 effect:).ti,ab. or (skin adj2 reaction:).ti,ab. or (distress* or discomfort* or fright* or anxious).ti,ab.	94,127	Pain terms
2	Back/ or upper extremity/ or arm/ or lumbosacral plexus/ or deltoid muscle/ or quadriceps muscle/ or immunization/ or immunization schedule/ or immunization programs/ or immunotherapy/ or (immunization: or immunisation:).mp. or (simultaneous or sequential).ti,ab. or (deltoid or thigh).ti,ab.	21,918	Injection site or type of immunization
3	Injections/ or injection sites/ or injections, intradermal/ or injections, intramuscular/ or injections, subcutaneous/ or injections, jet/ or needles/ or (needle: adj2 (gauge: or length: or thick: or angle: or size:)).ti,ab. or injections, jet/ or biolistics/ or ((needle: or inject: or vaccinat:) adj2 (technique: or technic: or aspirat: or angle: or speed: or slow: or rapid: or order:)).ti,ab. or massage:.mp. or (pressure or cuddling or cuddle: or hold: or ices or ice or iced or cold or hot or temperature).ti,ab. or (freezing or freeze or freezes).ti,ab. or refrigeration/ or (shot adj2 blocker).ti,ab. or exp vaccines/	69,634	Needle types or techniques or pain soothers
4	Exp evaluation research/ or clinical trials/ or double-blind studies/ or intervention trials/ or preventive trials/ or single-blind studies/ or therapeutic trials/ or triple-blind studies/ or ((random: adj2 control: adj2 trial:) or (random: adj2 clinic: adj2 trial:)).ti,ab. or ((clinical: adj5 trial:) or random: or ((singl: or doubl: or tripl: or trebl:) adj5 (mask: or blind:)) or (control: adj5 group:) or (quasi adj5 randomiz:) or (quasi adj5 randomis:)).ti,ab.	123,553	Study design/ methodology terms
5	1 and 2 and 3 and 4	138	Base clinical set

(continued)

Appendix (continued).

Set	History	Results	Comments
6	Limit 5 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)	48	Age group limit
7	5 and (neonat: or newborn: or infan: or child: or adolescen: or teen:).mp.	55	Age group textwords
8	6 or 7	55	Final results
Cochrane Central Register of Controlled Trials Search Strategy (3rd Quarter, 2008)			
1	Pain measurement/ or exp pain/ or antibody formation/ or crying/ or anxiety/ or fear/ or panic/ or (adverse adj2 effect:).ti,ab. or (side adj2 effect:).ti,ab. or (skin adj2 reaction:).ti,ab. or (distress* or discomfort* or fright* or anxious).ti,ab.	68,606	Pain terms
2	Back/ or lumbosacral region/ or sacrococcygeal region/ or upper extremity/ or arm/ or muscle, skeletal/ or quadriceps muscle/ or (deltoid or thigh).ti,ab. or immunization/ or immunization, passive/ or adoptive transfer/ or immunotherapy, adoptive/ or immunization schedule/ or immunization, secondary/ or immunotherapy, active/ or vaccination/ or mass immunization/ or (simultaneous or sequential).ti,ab.	14,137	Injection site or type of immunization
3	Needles/ or (needle: adj2 (gauge: or length: or thick: or angle: or size:)).ti,ab. or injections/ or injections, intramuscular/ or injections, subcutaneous/ or injections, intradermal/ or injections, jet/ or biolistics/ or ((needle: or inject: or vaccinat:) adj2 (technique: or technic: or aspirat: or angle: or speed: or slow: or rapid: or order:)).ti,ab. or massage:.mp. or (pressure or cuddling or cuddle: or hold: or ices or ice or iced or cold or hot or temperature).ti,ab. or (freezing or freeze or freezes).ti,ab. or refrigeration/ or (shot adj2 blocker).ti,ab. or exp vaccines/	62,733	Needle types or techniques or pain soothers
4	1 and 2 and 3	706	Base clinical set
5	4 and human*.mp.	692	Limit to human
6	5 and (neonat: or newborn: or infan: or child: or adolescen: or teen:).mp. (328)	328	Age group textwords and final results