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Pharmacological and Combined Interventions to Reduce Vaccine Injection Pain in Children and Adults

Systematic Review and Meta-Analysis

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Background: This systematic review assessed the effectiveness and safety of pharmacotherapy and combined interventions for reducing vaccine injection pain in individuals across the lifespan.

Design/Methods: Electronic databases were searched for relevant randomized and quasi-randomized controlled trials. Self-reported pain and fear as well as observer-rated distress were critically important outcomes. Data were combined using standardized mean difference (SMD) or relative risk with 95% confidence intervals (CI).

Results: Fifty-five studies that examined breastfeeding (which combines sweet-tasting solution, holding, and sucking), topical anesthetics, sweet-tasting solutions (sucrose, glucose), vapocoolants, oral analgesics, and combination of 2 versus 1 intervention were included. The following results report findings of analyses of critical outcomes with the largest number of participants. Compared with control, acute distress was lower for infants breastfed: (1) during vaccination (n = 792): SMD −1.78 (CI, −2.35, −1.22) and (2) before vaccination (n = 100): SMD −1.43 (CI, −2.14, −0.72). Compared with control/placebo, topical anesthetics showed benefit on acute distress in children (n = 1424): SMD −0.91 (CI, −1.36, −0.47) and self-reported pain in adults (n = 60): SMD −0.85 (CI, −1.38, −0.32). Acute and recovery distress was lower for children who received sucrose (n = 2071): SMD −0.76 (CI, −1.19, −0.34) or glucose (n = 818): SMD −0.69 (CI, −1.03, −0.35) compared with placebo/no treatment. Vapocoolants reduced acute pain in adults [(n = 185), SMD −0.78 (CI, −1.08, −0.48)] but not children. Evidence from other needle procedures showed no benefit of acetaminophen or ibuprofen. The administration of topical anesthetics before and breastfeeding during vaccine injections showed mixed results when compared with topical anesthetics alone. There were no additive benefits of combining glucose and non-nutritive sucking (pacifier) compared with glucose or non-nutritive sucking (pacifier) alone or breastfeeding and sucrose compared with breastfeeding or sucrose alone.

Conclusions: Breastfeeding, topical anesthetics, sweet-tasting solutions, and combination of topical anesthetics and breastfeeding demonstrated evidence of benefit for reducing vaccine injection pain in infants and children. In adults, limited data demonstrate some benefit of topical anesthetics and vapocoolants.

Key Words: pain management, randomized controlled trial, systematic review, vaccination

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The availability of vaccines has been a major breakthrough in the field of medicine, and vaccination programs have been the most cost-effective way of reducing the burden of communicable diseases. Despite the proven benefits of vaccination, many individuals globally have not reaped its benefits. Therefore, as part of an on-going effort to improve vaccination rates, the World Health Organization and their partners have developed the "Global Vaccination Action Plan" with the goal to improve vaccination compliance and reduce mortality from communicable diseases throughout an individual's lifespan.[1] As more vaccines become available and incorporated into vaccination schedules, individuals are subjected to an increasing number of injections. Vaccine injections are the

most common source of iatrogenic pain in children and adults and an important contributing factor to non-compliance with vaccination.[2–4] Pain associated with vaccination is now recognized as an important adverse event following immunization, and managing pain should therefore be part of every vaccination.[5]

Over the last several decades, numerous strategies including pharmacological, physical, procedural, process, and psychological interventions have been evaluated to mitigate the pain from vaccine injections.[6] Despite the effectiveness of many of these interventions, they are not routinely used by health care providers in clinical practice.[7] Pharmacological and combined interventions in particular, are rarely used due to barriers to implementation such as uncertainty about their effectiveness, concerns regarding adverse consequences, time commitment, and potential cost.

In a previous systematic review published on this topic in 2009,[8] evidence was found to support several interventions that were then incorporated into a clinical practice guideline for vaccination pain management in children.[6] Since that analysis, new literature has been published, including evaluation of combined interventions. Hence, there was a need to update the review. In addition, the previous synthesis was limited to children and it was deemed necessary to expand the synthesis to adults. Therefore, the HelpELiminatePain in KIDS (HELPinKIDS) team made a decision to expand the scope of the synthesis to include the literature on adult populations (HELPinKids&Adults).

The objective of this systematic review was to assess the effectiveness and safety of combined interventions and pharmacotherapy in reducing the pain associated with vaccine injections in children and adults. The interventions evaluated included: (1) breastfeeding (which combines sweet-tasting solution, sucking, and holding [physical comfort]), either before or during vaccine injections; (2) topical anesthetics; (3) sweet-tasting solutions (sucrose and glucose); (4) vapocoolants; (5) oral analgesics (acetaminophen and ibuprofen); and (6) 2 interventions versus 1 intervention (ie, topical anesthetic and breastfeeding vs. topical anesthetics alone; sweet-tasting solutions and non-nutritive sucking vs. sweet-tasting solutions or non-nutritive sucking alone; or sweet-tasting solutions and breastfeeding vs. breast feeding or sweet-tasting solutions alone).

METHODS

The methodological details used to perform this systematic review are described elsewhere.[9] In short, both the Grading of Assessments, Recommendations, Development, and Evaluation (GRADE)[10] and Cochrane[11] methodologies guided the review.

Search Strategy

A comprehensive literature search was performed using the search strategy developed by the authors based on their content expertise and in consultation with an academic librarian for the following databases: EMBASE, Medline, PsycINFO, CINAHL, and ProQuest Dissertations & Theses Global (inception—February 26, 2015). No language restrictions were applied. The titles and abstracts of the articles were screened and retrieved articles were assessed for eligibility by 2 reviewers (V.S., A.T.). In addition, reference lists from eligible articles were reviewed to identify additional studies.

Inclusion/Exclusion Criteria

This review included: (1) children and adults undergoing vaccine injections in any setting (eg, hospital, community) or if not undergoing vaccine injections, the closest related needle procedure or context (eg, venipuncture, venous cannulation, needle puncture into a subcutaneous [SC] port); and (2) randomized controlled trials (RCTs) or studies with a quasi-randomized study design. We included studies published as full or short reports, as well as published academic theses. We excluded studies in which the analgesic intervention or the outcome of interest was not clearly defined, published abstracts, letters, commentaries, and editorials.

Clinical Questions

The included clinical questions and outcomes of interest (Table 1) were prioritized by the HELPinKids&Adults team.

Outcomes of Interest

As per the GRADE methodology, outcomes of interest were categorized as critical and important outcomes for inclusion in the review and data for these outcomes were extracted from the eligible studies. The critically important and important outcomes for included clinical questions are shown in Table 1. Self-report of pain was prioritized as the critically important outcome when self-report of pain was possible (eg, child over 3 y of age). For children under 3 years, distress was the critically important outcome. Fear was prioritized as a critical outcome only for topical anesthetics and required the ability to self-report.

For health care professionals, safety (adverse consequences), fidelity, feasibility, and preference are major issues that need to be addressed before implementing evidence-based interventions in practice. Therefore, the above-listed outcomes were prioritized as important outcomes and are included in the presentation of outcomes. For topical local anesthetics, we examined transient changes in skin color (pallor or erythema), edema and effects on the immune response. Episodes of aspiration, vomiting, cyanosis, and respiratory change during and after the procedure were assessed for breastfeeding; episodes of choking, coughing, gagging, nausea, vomiting, and physiological instability were assessed for sweet-tasting solutions (eg, sucrose, glucose), and oral analgesics. For vapocoolants, pain during application and skin reactions were evaluated. Data on immunogenicity was examined for oral analgesics. We also reported on the fidelity (use or compliance with the intervention), feasibility (ease of adoption in clinical practice), and preferences (choosing one intervention over the other) for each of the intervention as available.

Quality Assessment

The methodologic quality of the studies was assessed by 2 reviewers using the Cochrane Collaboration's Risk of Bias tool, and the overall summary assessment of the Risk of Bias was designated for individual studies.[11]

Data Abstraction and Synthesis

Data were abstracted on a predesigned form by 2 reviewers (V.S., A.T.) and checked for accuracy. The trials had to include the data necessary for pooling in a meta-analysis, such as means and standard deviations (SDs), and

TABLE 1. Clinical Questions and Outcomes

Clinical Questions	Critical Outcomes*	Important Outcomes
Pharmacological interventions		
Should breastfeeding be used during vaccine injections in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
If breastfeeding is not used during vaccine injections, should breastfeeding be used before vaccine injections in children 0-2 y?	Distress	Procedure outcome, parent fear, use of intervention, compliance, preference, satisfaction
Should topical anesthetics be applied before vaccine injections in children 0-12 y?	Pain, distress, fear	Procedure outcome, safety, parent fear, use of intervention, compliance, memory, preference, satisfaction
Should topical anesthetics be applied before vaccine injections in adolescents > 12 y and adults?	Pain	Distress, fear, procedure outcome, safety, use of intervention, compliance, memory, preference, satisfaction
Should topical anesthetics be used before vaccine injections in combination with breastfeeding during vaccine injections (rather than topical anesthetics or breastfeeding alone) in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
Should sucrose solution be given before vaccine injections in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
Should glucose solution be given before vaccine injections in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
Should sweet-tasting solutions (sucrose, glucose) be used before vaccine injections in combination with non-nutritive sucking (finger/thumb, pacifier) during vaccine injections (rather than sweet-tasting solutions or non-nutritive sucking alone) in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
Should breastfeeding and sweet-tasting solutions (sucrose, glucose) be combined together before vaccine injections (rather than breastfeeding or sweet-tasting solutions alone) in children 0-2 y?	Distress	Procedure outcome, safety, parent fear, use of intervention, compliance, preference, satisfaction
Should vapocoolants be applied before vaccine injections in children 0-3 y?	Distress	Parent fear, procedure outcome, safety, compliance, preference, satisfaction
Should vapocoolants be applied before vaccine injections in children > 3-17 y?	Pain	Distress, fear, parent fear, procedure outcome, safety, compliance, memory, preference, satisfaction
Should vapocoolants be applied before vaccine injections in adults?	Pain	Distress, fear, procedure outcome, safety, compliance, memory, preference, satisfaction
Should acetaminophen be given before vaccine injections in individuals of all ages?	Pain, distress	Fear, safety, compliance, preference, satisfaction
Should ibuprofen be given before vaccine injections in individuals of all ages?	Pain, distress	Fear, safety, compliance, preference, satisfaction

*Distress is the critical outcome in the absence of data for pain, fear, or both in individuals incapable of self-report (eg, infants).

the prioritized outcomes had to be assessed by the child or adult (self-report) or by others using validated tools.[12,13]

Modification of the original data was done as needed on a predefined, restricted basis according to established methods.[14] For example, means (and SDs) were calculated from medians, ranges, and 95% confidence intervals (CIs), or estimated from graphs.[14] As pain, distress, or both were assessed at multiple timepoints in the included studies, the data were standardized and analyzed as follows (according to the procedure phase): (1) the preprocedure phase, which occurred postintervention but before vaccine injection(s); (2) the acute procedure phase (within the first minute of needle puncture and vaccine injection); and (3) the recovery procedure phase (1 to 5 min after vaccine injection(s)) to determine the effectiveness of an intervention.

Established methods were used to pool data before inclusion in the meta-analysis if data were available from multiple observers evaluating the same outcome (eg, parent-rated or clinician/researcher-rated child distress) or if available at multiple timepoints within the same procedure phase (eg, acute distress measured every 15 s within the first minute of vaccine injection).[15] The scores were first standard on a scale of 0 to 10, using an estimated correlation of 0.25.[16] This process allowed all the data pertaining to an outcome to contribute to the summary statistic included in the meta-analysis and reduce bias from either "selecting/picking the data" from individual studies included in the meta-analysis.[9] Authors of trials were contacted for further details or provision of original data if the published report contained insufficient information. Missing data were not imputed.

All statistical analyses were conducted using Review Manager (RevMan) version 5.2, the statistical software provided by the Cochrane Collaboration (Copenhagen, Denmark).[11] Results are presented as standardized mean difference (SMD) and 95% CI or relative risk (RR) and 95% CI as appropriate. All meta-analyses were conducted using a random-effects model. Statistical heterogeneity was assessed using I^2 and χ^2 tests.[11] If appropriate, a sensitivity analysis was performed by including and excluding studies

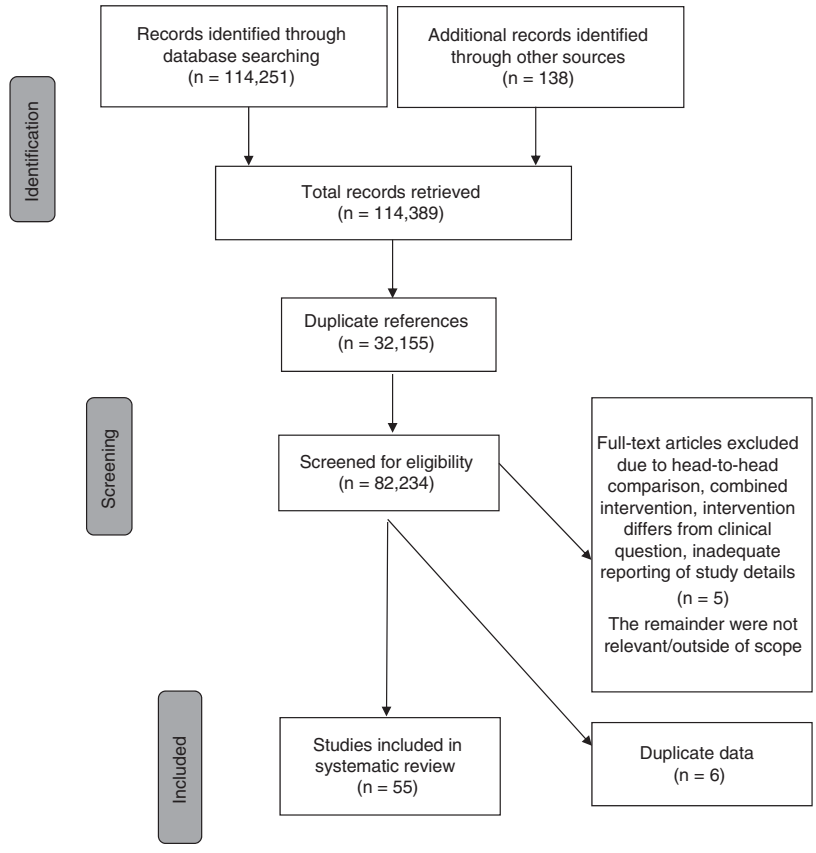

FIGURE 1. Flow of studies.

with a high likelihood of bias, as assessed by the Risk of Bias tool.[11] Funnel plots were performed to assess for the possibility of publication bias if there were sufficient trials (> 10).[11]

Separate analyses were planned for the following interventions based on the age of the participants and/or attributes of the interventions: (1) breastfeeding (0 to 2 y); (2) topical anesthetics (children 0-12 y, adolescents > 12 y and adults); (3) sweet tasting solutions (0-2 y); and (4) vapocoolants (children 0 to 3 y, children older than 3 to 17 y, and adults). In addition, separate analyses were conducted to account for differences in the timing of administration of interventions (ie, breastfeeding immediately before, during, and after the procedure vs. breastfeeding prevaccine injection). Finally, subgroup analyses were planned to examine the impact of sucrose concentration according to 3 dose intervals: low concentration (< 20%), moderate concentration (20% to < 50%), and high concentration (≥ 50%). Analyses are presented according to these decisions. Post-hoc additional analyses were carried out to examine the effects of study methodology, heterogeneity, or both.

Evidence Profiles and Summary of Findings

The GRADE profiler software (version 3.6.1) was used to create evidence profiles and summary of findings tables in which all judgments and information pertaining to the evaluation of the quality of evidence were recorded. The quality of evidence could be rated as high, moderate, low, and very low. If a benefit was noted across all the critical outcomes, the intervention was said to be beneficial; if the results were inconsistent, the intervention was said to have mixed benefit. Interventions without statistical evidence of benefit were said to have no evidence of benefit.

RESULTS

The database searches yielded 114,251 references and an additional 138 references were identified separately from manual searches. All references were stored in an EndNote library that identified 32,155 duplicates. The remaining 82,234 references were reviewed by 2 of the authors (V.S., A.T.) against the inclusion criteria.[9] Five studies were excluded after reviewing the full manuscript as it included: (1) combined interventions versus control (n = 1)[17]; (2) a no comparator group (n = 2),[18,19]; (3) did not include intervention according to the clinical question (n = 1)[20]; and (4) the procedure was SC injection of normal saline (n = 1).[21]

Sixty-one studies investigating pharmacological and combined interventions were included in the review.[22–82] In 6 cases, multiple citations were identified for the same study; 2 of these included a dissertation[47,59] and published manuscript with the same data,[46,58] whereas the other 4 included multiple citations for the same study.[28,31,32,63] A total of 55 studies were included in this review. The study selection log is shown in Figure 1.

Characteristics of included studies are described in Table 2. Except for 2 studies[39,82] that used cross-over designs, the trials used between-groups (parallel) designs. All studies provided data for ≥ 2 treatment arms. The

TABLE 2. Characteristics of the Trials Included in the Systematic Review

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
Should breastfeeding be used during vaccine injections in children 0-2 y?				
Abdel Razek 2009,[22] Jordan	Vaccine NR; no injection details	N = 120; infants 1-12 mo; between-groups design; multicenter, maternal and child health centers	Breastfeeding during and after the procedure (n = 60) or Control (no intervention and restrained by the mother during injection) (n = 60)	Distress: NIPS, Wong-Baker FACES Pain Rating Scale, Cry
Dilli 2009 (1),[23] Turkey	Hepatitis B injections at 0-2 wk, 1 and 6 mo or MMR at 12 mo; BCG 2 mo; DTP-IPV-Hib 2, 4, 6, and 16-24 mo; 16- or 25-mm needle; single or multiple injections; IM or SC or ID; vastus lateralis or deltoid	N = 250; infants and children 0-48 mo; between-groups design; single center, hospital well child unit	Infants < 6 mo: Breastfeeding 30-60 s before and during the procedure (n = 73) or Control (no intervention) (n = 85) Infants and children 6-48 mo†: Sucrose 12% 2 mL 2 min before the procedure (n = 34) or Lidocaine-prilocaine cream 5% 1 g × 1 h before the procedure; applied on lateral region of right thigh or deltoid (n = 24) or Control (no intervention) (n = 30)	Distress: NIPS, Cry
Efe 2007,[24] Turkey	DTaP 0.5 mL IM; 26-G, 15.9-mm needle; 90-degree angle; anterior thigh	N = 66; infants 2-4 mo; between-groups design; single center, hospital healthy child clinic	Breastfeeding before, during, and after the procedure (n = 33) or Control (swaddled in the bassinets during the procedure and mother encouraged to soothe the infant verbally) (n = 33)	Distress: Cry
Goswami 2013 (1)[25] India	wDPT 0.5 mL IM; 23-G, 25.4-mm needle; 90-degree angle; anterolateral thigh	N = 120; infants < 3 mo; between-groups design; single center, hospital immunization clinic	Breastfeeding starting 2 min before and throughout the procedure (n = 40) or Dextrose 25% 2 mL 2 min before procedure (n = 40)† or Distilled water 2 mL 2 min before procedure (n = 40)	Distress: MFCS, Cry
Iqbal 2014,[26] Pakistan	BCG 0.05 mL ID; 25-26 G short beveled needle; lower half of the right deltoid muscle	N = 150; full-term neonates < 48 h; between-groups design; single center, nursery in a hospital	Breastfeeding 2 min before and throughout the procedure (n = 75) or Control (infant placed on a table with mother next to the infant and helping in holding and soothing verbally) (n = 75)	Distress: DAN
Modarres 2013,[27] Iran (same as Modarres 2007)	Hepatitis B 0.5 mL IM; 23-G, 1-inch needle; 90-degree angle; anterior thigh	N = 130; full-term neonates < 24 h; between-groups design single center, nursery in a hospital	Breastfeeding 2 min before, during, and after the procedure (n = 65) or Control (held in the mother's arms) (n = 65)	Distress: DAN
Shah Ali 2009,[29] Iran (same as Taavoni 2009, 2010 and 2010a)	DPT 0.5 mL IM; 23-G, 25-mm needle	N = 76; infants 2-4 mo; between-groups design; multicenter, primary care practices	Breastfeeding starting 2 min before, during, and 15 s postinjection (n = 38) or	Distress: MBPS

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			Mother holding infant starting 2 min before, during, and 15 s postinjection (n = 38)	
Taavoni 2009,[30] Iran (same as Taavoni 2010 and 2010a, and Shah Ali 2009)	DPT 0.5 mL IM; 23-G, 25-mm needle	N = 76; infants 2-4 mo; between-groups design; multicenter, primary care practices	Breastfeeding starting 2 min before, during, and 15 s postinjection (n = 38) or Control (infant supine) (n = 38)	Distress: MBPS
Thomas 2011,[33] India	DPT IM; no injection details	N = 40; infants 5-15 wk; between-groups design; single center, hospital clinic	Breastfeeding 2 min before and during procedure (n = 20) or Control (no intervention) (n = 20)	Distress: MNIPS
If breastfeeding is not used during vaccine injections, should breastfeeding be used before vaccine injections in children 0-2 y?				
Achema 2011 (1),[34] Nigeria	DPT IM; no injection details	N = 60; infants 6 wk; between-groups design; multicenter, primary health centers	Breast feeding 1 h before the procedure (n = 20) or Lidocaine-prilocaine cream applied 1 h before the procedure (n = 20)† or Control (mothers held and cuddled their infant before the procedure) (n = 20)	Distress: APS, PAINAD
Sahebihagh 2011 (1),[35] Iran	DPT, hepatitis B vaccine IM; no injection details	N = 120; infants < 3 mo; between-groups design; multicenter, health centers	Breastfeeding based on infant's appetite before the procedure (n = 30) or Sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30)† or Breast feeding based on infant's appetite followed by sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30)† or Control (no intervention) (n = 30)	Distress: NIPS, Cry
Should topical anesthetics be applied before vaccine injections in children 0-12 y?				
Abuelkheir 2014,[36] Saudi Arabia	DTP, HAV, influenza, IPV, MCV, measles, MMR, PCV13, pentavalent DTP-HBV-HIB, tetravalent DTP-HIB, varicella IM or SC; lateral region of the thigh in children < 1 y; deltoid for children ≥ 1 y	N = 216 children 2 mo to 6 y; between-groups design; single center, hospital paediatric clinic	Lidocaine-prilocaine cream 5% 0.5 g, application time range (19-103 min), (n = 107) or Placebo cream 0.5 g, application time range (32-97 min), (n = 109)	Distress: MBPS, VAS, Cry
Achema 2011 (2),[34] Nigeria	DPT IM; no injection details	N = 60; infants 6 wk; between-groups design; multicenter, primary health centers	Breast feeding 1 h before the procedure (n = 20)† or Lidocaine-prilocaine cream 5% (dose NR) applied 1 h before the procedure (n = 20) or Control (mothers held and cuddled their infant before the procedure) (n = 20)	Distress: APS, PAINAD

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
Basiri-Moghadam 2014,[37] Iran	DPT 0.5 mL IM; 23-G, 25-mm needle; vastus lateralis	N = 50; infants 4 mo; between-groups design; single center; clinic	Lidocaine-prilocaine cream 5% 2 g 1 h before the procedure (n = 16) or Rattle shaken 30 s before and 15 s after the procedure (n = 16)† or Control (n = 18)	Distress: MBPS
Cassidy 2001,[38] Canada	DPTP 1 mL IM; 25-G, 15-mm needle; 90-degree angle; mid-deltoid	N = 161; children 4-6 y; between-groups design; multicenter, urban and rural outpatient clinics	Lidocaine-prilocaine patch 5% 1 g 1-2 h and removed no more than 10 min before the procedure (n = 83) or Placebo patch 1 g 1-2 h and removed no more than 10 min before the procedure (n = 76)	Pain: FPS, VAS, CFCS, CHEOPS
Cohen 1999 (2),[39] USA	Hepatitis B IM; no injection details	N = 39; children 9-11 y; cross-over design; single center, school health clinic	Lidocaine-prilocaine cream 5% 2 g 1 h before the procedure (n = 34) or Nurse coaching and movie distraction (n = 34)† or Control (standard care) (n = 34)	Pain: VAS, CAMPIS-R
Cohen 2006 (3,4),[40] USA	Hib IM, MMR, and Varivax SC; no injection details	N = 84; infants evaluated at 12 and 18 mo; between-groups longitudinal design; single center, rural health clinic	Distraction (nurses trained on implementation of the distraction protocol) (n = 28)† or Lidocaine-prilocaine cream 5% 2 g 1 h before the procedure (n = 28) or Control (standard care provided by nurses and included some distraction) (n = 28)	Distress: MBPS
Cohen Reis 1997 (1),[41] USA	DTaP 0.5 mL IM; 26-G, ½-inch needle; 90-degree angle; deltoid	N = 62; children 4-6 y; between-groups design; single center, hospital primary care center	Lidocaine-prilocaine cream 5% 2.5 g for 60 min + distraction (blow on a pinwheel held by themselves or their parents) (n = 21) or Vapocoolant (Fluorimethane) spray on a cotton ball applied for 15 s immediately before the procedure + distraction (n = 20)† or Distraction alone (n = 21)	Pain: Bieri FPS, VAS
Dilli 2009 (2),[23] Turkey	Hepatitis B injections at 0-2 wk, 1 and 6 mo or MMR at 12 mo; BCG 2 mo; DTP-IPV-Hib 2, 4, 6, and 16-24 mo; 16- or 25-mm needle; single or multiple injections; IM, SC, or ID vastus lateralis or deltoid	N = 250; infants and children 0-48 mo; between-groups design; single center, hospital well child unit	Infants < 6 mo†: Breastfeeding 30-60 s before and during the procedure (n = 73) or Control (no intervention) (n = 85) Infants and children 6-48 mo: Sucrose 12% 2 mL 2 min before the procedure (n = 34)† or Lidocaine-prilocaine cream 5% 1 g 1 h before the procedure (n = 24) or Control (no intervention) (n = 30)	Distress: NIPS, Cry

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
Gupta 2013 (1),[42] India	wDPT 0.5 mL IM; 23-G, 1-inch needle; anterolateral thigh	N = 90; infants < 3 mo; between-groups design; single center, immunization clinic	Lidocaine-prilocaine cream 5% 1 g 1 h + breast feeding 2 min before the procedure (n = 30)† or Lidocaine-prilocaine cream 5% 1 g 1 h + 2 mL distilled water 2 min before the procedure (n = 30) or Placebo cream 1 g 1 h + 2 mL distilled water 2 min before the procedure (n = 30)	Distress: MFCS, Cry
Halperin 2000,[43] Canada	MMR 0.5 mL SC; 25-G, 15-mm needle; mid-thigh	N = 160; infants and children ≥ 1 y; between-groups design; single center, ambulatory clinic	Lidocaine-prilocaine patch 5% 1 g 1-3 h before the procedure (n = 80) or Placebo patch 1 g 1-3 h before the procedure (n = 80)	Distress: MBPS, Cry
Halperin 2002,[44] Canada	Part A: DPTaP-IPV-Hib and hepatitis B 0.5 mL, IM; 23-G, 25-mm needle Part B: DPTaP-IPV-Hib 0.5 mL at 2, 4, 6 mo and hepatitis B 0.5 mL IM at < 2, 2, 6 mo; 25- or 23-G (6 mo), 25-mm needle	N = 165 Part A (N = 109); infants 6 mo Part B (N = 56): infants 0-2 mo; between-groups design; multicenter, ambulatory clinics	Part A: Lidocaine-prilocaine patch 5% 1 g 1-3 h before the procedure (n = 54) or Placebo patch 1 g 1-3 h before the procedure (n = 55) Part B: Lidocaine-prilocaine patch 5% 1 g 1-3 h before the procedure (n = 28) or Placebo patch 1 g 1-3 h before the procedure (n = 28)	Distress: MBPS
Kumar (thesis 2014),[45] India	DPT-HiB-hepatitis IM; 25-G, 1-inch needle; 90-degree angle; anterolateral thigh	N = 300; infants 6 wk to 6 mo; between-groups design; single center, immunization clinic	Lidocaine-prilocaine cream 5% 1 g 1 h before the procedure (n = 75) or Lidocaine spray 10% sprayed at the injection site 10 s before the procedure (n = 75)† or Lidocaine spray 10% + vapocoolant (benzocaine 0.36%, polyvinyl polymer 2.52% in propellant solvent) sprayed at the injection site 10 s before the procedure (n = 75)† or Control (topical spray of water at 4°C) sprayed at the injection site 10 s before the procedure (n = 75)	Distress: MBPS
O'Brien 2004 (thesis 2004),[46] Canada	MMR 0.5 mL SC; 25-G, 16-mm needle; deltoid	N = 120; infants > 12 mo; between-groups design; multicenter, outpatient clinics	Amethocaine gel 4% 1 g 30-45 min before the procedure (n = 61) or Placebo 1 g 30-45 min before the procedure (n = 59)	Distress: MBPS, NFCS, VAS, Cry
Taddio 1994,[48] Canada	DPT 0.5 mL IM; 25-G, 16-mm needle; mid-thigh	N = 100; infants 4-6 mo; between-groups design; single center, outpatient clinic	Lidocaine-prilocaine cream 5% 2.5 g 1-2 h before the procedure (n = 49) or	Distress: MBPS, VAS, Cry

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			Placebo 2.5 g 1-2 h 1 h before the procedure (n = 47)	
Uhari 1993,[49] Finland	DPT IM (98% of children, 2% NR); no injection details	N = 155; infants 3-28 mo; between-group design; multicenter, outpatient clinics	Lidocaine-prilocaine cream 5% 1 h before the procedure (n = 79) or Placebo cream 1 h before the procedure (n = 76)	Distress: VAS
Should topical anesthetics be applied before vaccine injections in adolescents > 12 y and adults?				
Hansen 1993,[50] Denmark	MMR SC; no injection details	N = 118; children 11-15 y; between-groups design; multicenter, outpatient clinics	Lidocaine-prilocaine cream 5% 1 g 1 h before the procedure (n = 58) or Placebo (coconut oil cream) 1 g 1 h before the procedure (n = 59)	Distress: Likert scale
Taddio 1992,[51] Canada	Influenza virus vaccine (Fluzone) 0.5 mL IM; 22-G, 1-inch needle; arms	N = 60; adult volunteers; between-groups design; single center, hospital setting	Lidocaine-prilocaine cream 5% 2.5 g 1-2 h before the procedure (n = 29) or Placebo 2.5 g 1-2 h before the procedure (n = 31)	Pain: MBPS
Should topical anesthetics be used before vaccine injections in combination with breastfeeding during vaccine injections (rather than topical anesthetics or breastfeeding alone) in children 0-2 y?				
Gupta 2013 (2),[42] India	wDPT 0.5 mL IM; 23-G, 1-inch needle; anterolateral thigh	N = 90; infants < 3 mo; between-groups design; single center, immunization clinic	Lidocaine-prilocaine cream 5% 1 g 1 h + breast feeding 2 min before the procedure (n = 30) or Lidocaine-prilocaine cream 5% 1 g 1 h + 2 mL distilled water 2 min before the procedure (n = 30)† or Placebo cream 1 g 1 h + 2 mL distilled water 2 min before the procedure (n = 30)	Distress: MFCS, Cry
Should sucrose solution be given before vaccine injections in children 0-2 y?				
Allen 1996 (1-12),[52] USA	1 injection: hepatitis B 2 wk and 9 mo; DTP 18 mo 2 injections: DTP and Hib 2 and 6 mo; MMR and Hib 15 mo 3 injections: DTP, Hib, hepatitis B 4 mo; SC, thigh	N = 285; infant age categories: 2 wk (n = 50); 2 mo (n = 44); 4 mo (n = 50); 6 mo (n = 46); 9 mo (n = 28); 15 mo (n = 30); 18 mo (n = 37); between-groups design; single center, ambulatory clinic	Sucrose 12% 2 mL administered 2 min before the procedure or Sterile water 2 mL administered 2 min before the procedure or Control (no intervention) n for each group NR	Distress: Cry
Barr 1995,[53] Canada	DTP, IM; thigh	N = 66; infants evaluated at 2 and 4 mo, between-groups design; longitudinal study single center, pediatric practice	Sucrose 50% 3 doses of 250 μL on tongue at 30-s intervals, injection administered immediately after the last dose (n = 30) or Sterile water 3 doses on the tongue at 30-s intervals, injection administered immediately after the last dose (n = 27)	Distress: Cry
Chattopadhyay 2011,[54] India	DPT IM; anterolateral, mid-thigh	N = 60; infants 6-11 mo; between-groups design; single center, hospital maternal and child health clinic	Sucrose 2 mL administered over 30 s, injection immediately thereafter (n = 30) or Water 2 mL administered over 30 s, injection immediately thereafter (n = 30)	Distress: NIPS

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
Dilli 2009 (3),[23] Turkey	Hepatitis B injections at 0-2 wk, 1 and 6 mo or MMR at 12 mo; BCG 2 mo; DTP-IPV-Hib 2, 4, 6, and 16-24 mo; 16- or 25-mm needle; single or multiple injections; IM, SC or ID; vastus lateralis or deltoid	N = 250; infants and children 0-48 mo; between-groups design; single center, hospital well child unit	Infants < 6 mo†: Breastfeeding 30-60 s before and during the procedure (n = 73) or Control (no intervention) (n = 85) Infants and children 6-48 mo: Sucrose 12% 2 mL 2 min before the procedure (n = 34) or Lidocaine-prilocaine cream 1 g × 1 h before the procedure; applied on lateral region of right thigh or deltoid (n = 24)† or Control (no intervention) (n = 30)	Distress: NIPS, Cry
Harrington 2012 (3,4),[55] USA	Hepatitis B, DTP-IPV-Hib, PCV; 0.5 mL/vaccine IM; 23-G, 1.59-cm needle; 90-degree angle; anterolateral thigh; sequential injections	N = 230; infants 2-4 mo; between-groups design; single center, hospital clinic	Sucrose 24% 2 mL 2 min before the procedure + combined physical intervention (swaddling, side/stomach position, shushing, swinging, and sucking) (n = 58) or Sucrose 24% 2 mL 2 min before the procedure + control (no intervention) (n = 58) or Water 2 mL 2 min before the procedure + combined physical intervention (as described above) (n = 58) or Water 2 mL 2 min before the procedure + control (no intervention) (n = 56)	Distress: Modified Riley Pain Scale
Harrison 2014 (1,2),[56] Australia	Hib, MCV IM, MMR, SC at 12 mo; varicella SC at 18 mo; no injection details	N = 29; infants 12 and 18 mo; between-groups design; single center, hospital immunization clinic	Sucrose 33% in 0.5 mL aliquots 2 min before first injection and then repeated 0.5 mL before each injection (n = 15) or Water in 0.5 mL aliquots 2 min before first injection and then repeated 0.5 mL before each injection (n = 14)	Distress: FLACC, Cry
Hatfield 2008,[57] USA	DTaP-hepatitis B-IPV followed 3 min later by Hib followed 2 min later by pneumococcal conjugate vaccine, IM; 25-G, 1-inch needle	N = 100; infants 2 and 4 mo; between-groups design; single center, ambulatory pediatric clinic	Sucrose 24% 0.6 mL/kg 2 min before + NNS using a pacifier 2 min before, during, and 7 min after the initial injection (n = 38) or Water 0.6 mL/kg 2 min before + NNS using a pacifier 2 min before , during, and 7 min after the initial injection (n = 45)	Distress: UWCH Pain Scale
Hatfield 2008a,[58] USA	DTaP-hepatitis B-IPV, Hib, and pneumococcal conjugate vaccine, IM; 25-G, 1-inch needle	N = 40; infants 2 and 4 mo; between-groups longitudinal design; single center, ambulatory pediatric clinic	Sucrose 24% 0.6 mL/kg 2 min before + NNS using a pacifier 2 min before, during, and 3 min postinjection (n = 20) or	Distress: UWCH Pain Scale

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			Water 0.6 mL/kg + NNS using a pacifier 2 min before, during, and 3 min postinjection (n = 20)	
Lewindon 1998,[60] Australia	Oral polio, DTP, Hib, IM; thigh	N = 110; infants 7-38 wk; between-groups design; single center, ambulatory clinic	Sucrose 75% 2 mL over 15 s followed by the procedure (n = 54) or Water 2 mL over 15 s followed by the procedure (n = 53),	Distress: VAS, Cry
Liaw 2011 (2),[61] China	Hepatitis B vaccine IM; 90-degree angle; vastus lateralis; aspiration before injection	N = 165; newborns after second-third day of life; between-groups design; single center, nursery in a hospital	Non-nutritive sucking using standard silicone newborn pacifier 2 min before the procedure (n = 55)† or Sucrose 20% 2 mL using a syringe 2 min before the procedure (n = 55) or Control (gentle touch and verbal comfort) (n = 55)	Distress: NFCS, Cry
Moradi 2012 (1,2),[62] Iran (same as Moradi 2012a)	Hepatitis B 0.5 mL, IM; no injection details	N = 91; newborns 1-2 d of age; between-groups design; single center, hospital setting	Sucrose 20% 2 mL 2 min before the procedure (n = 30) or Sucrose 50% 2 mL 2 min before the procedure (n = 30) or Water 2 mL 2 min before the procedure (n = 31)	Distress: NIPS
Mowrey (thesis 2008),[64] USA	DTaP-IPV-Hib, hepatitis B, prevnar injections, IM; no injection details	N = 52; infants 2-6 mo; between-groups design; single center, hospital pediatric clinic	Sucrose 50% 2 mL 2 min before the procedure (n = 25) or Water 2 mL over 1 min (n = 24)	Distress: MBPS, Cry
Poulsen 2009,[65] Denmark	DTaP-IPV + Hib, IM; grey needle 0.4 × 19	N = 67; infants 3-9 mo; single center, hospital	Sucrose 12% 2 mL 2 min before the procedure (n = NR) or Water 2 mL 2 min before the procedure (n = NR)	Distress: NIPS (this study was not included in the meta-analysis for critical outcomes as scores NR)
Priambodo 2008,[66] Indonesia	wDPT, IM; anterolateral thigh	N = 86; infants 4-6 mo; between-groups design; multicenter, hospital outpatient clinic and public health centers	Sucrose 75% 2 mL 2 min before the procedure (n = 42) or Water 2 mL 2 min before the procedure (n = 44)	Distress: Cry
Ramenghi 2002 (1,2),[67] UK	DTP followed by Hib 3 min later, IM; thigh	N = 184; infants 7-25 wk; between-groups design; single center, immunization clinic	Sucrose 25% 2 mL 2 min before the procedure (n = 46) or Sucrose 50% 2 mL 2 min before the procedure (n = 45) or Hydrogenated glucose 40% 2 mL 2 min before the procedure (n = 46)† or Water 2 mL 2 min before the procedure (n = 47)	Distress: Cry
Sahebihagh 2011 (4),[35] Iran	DPT, hepatitis B vaccine IM; no injection details	N = 120 infants < 3 mo; between-groups design; multicenter, health centers	Breast feeding based on infant's appetite before the procedure (n = 30)† or Sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30)	Distress: NIPS, Cry

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			or Breast feeding based on infant's appetite followed by sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30)† or Control (no intervention) (n = 30)	
Soriano Faura 2003,[68] Spain	Hepatitis B or DPT IM; no injection details	N = 323; infants 1-6 mo; between-groups design; multicenter, pediatric clinics	Sucrose 75% 2 mL 1 min before the procedure (n = 165) or Water 2 mL 1 min before the procedure (n = 158)	Distress: Cry
Yilmaz 2014 (1,2),[69] Turkey	DTaP/HiB/IPV, pneumococcal and hepatitis A, IM; deltoid	N = 537; infants 16-19 mo; between-groups design; single center, hospital well child unit	Sucrose 75% 2 mL 2 min before the procedure (n = 179) or Sucrose 25% 2 mL 2 min before the procedure (n = 179) or Water 2 mL 2 min before the procedure (n = 179)	Distress: Cry, CHEOPS
Should glucose solution be given before vaccine injections in children 0-2 y?				
Chermont 2009 (4),[70] Brazil	Hepatitis B 0.5 mL IM; 25-G needle; anterolateral thigh	N = 640; newborn 12-72 h; between-groups design; single center, hospital maternity ward	Mother holding diaper-clad neonate on chest (skin-to-skin) + 1 mL water 2 min before, during, and 2 min after procedure (n = 160)† or Diaper-clad neonate in crib + 1 mL water (n = 160) or Mother holding diaper-clad neonate on chest (skin-to-skin) + 1 mL dextrose 25% solution 2 min before, during, and 2 min after procedure (n = 160)† or Diaper-clad neonate in crib + 1 mL dextrose 25% solution (n = 160)	Distress: NFCS, NIPS, PIPP
Golestan 2007 (1,2),[71] Iran	Hepatitis B; no injection details	N = 90; newborn < 24 h between-groups design; single center, hospital maternity ward	Glucose 50% 2 mL orally in < 1 min followed by the procedure 2 min later (n = 30) or Water 2 mL orally in < 1 min followed by the procedure 2 min later (n = 30) or Control (no intervention) (n = 30)	Distress: Cry
Goswami 2013 (2),[25] India	wDPT 0.5 mL IM; 23-G, 25.4-mm needle; 90-degree angle; anterolateral thigh	N = 120; infants < 3 mo; between-groups design; single center, hospital immunization clinic	Breastfeeding starting 2 min before and throughout the procedure (n = 40)† or Dextrose 25% 2 mL 2 min before procedure (n = 40) or Distilled water 2 mL 2 min before procedure (n = 40)	Distress: MFCS, Cry

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
Kassab 2012,[72] Jordon	DTP/HIB/IPV, Hib, IM; 21-G, 15.9-mm needle; 90-degree angle; anterolateral thigh	N = 120; infants 2 mo; between-groups design; multicenter, child health care centers	25% glucose 2 mL immediately before the procedure (n = 60) or Water 2 mL immediately before the procedure (n = 60)	Distress: MBPS, Cry
Mörelius 2009 (1,4),[73] Sweden	DPT-IPV-HiB 0.5 mL IM; anterolateral thigh	N = 98; infants 3 mo; between-groups design; single center, pediatric clinic	Water 1 mL using a syringe followed by pacifier before the procedure (n = 25) or Water 1 mL using a syringe before the procedure (n = 24) or Glucose 30% 1 mL using a syringe followed by pacifier before the procedure (n = 29) or Glucose 30% 1 mL using a syringe before the procedure (n = 20)	Distress: Cry
Thyr 2007,[74] Sweden	Infanrix, polio, Hib, IM; thigh	N = 110; infants evaluated at 3, 5 and 12 mo; between-groups design; longitudinal study; single center, ambulatory clinic	Glucose 30% 2 mL (0.6 g) 30 s before, during, and 10-30 s after the procedure (n = 55) or Sterile water 2 mL 30 s before, during, and 10-30 s after the procedure (n = 55)	Distress: Cry
Should sweet-tasting solutions (sucrose, glucose) be used before vaccine injections in combination with non-nutritive sucking (finger/thumb, pacifier) during vaccine injections (rather than sweet-tasting solutions or non-nutritive sucking alone) in children 0-2 y?				
Mörelius 2009 (3,4),[73] Sweden	DPT-IPV-HiB 0.5 mL IM; anterolateral thigh	N = 98; infants 3 mo; between-groups design; single center, pediatric clinic	Water 1 mL using a syringe followed by pacifier (n = 25) or Water 1 mL using a syringe (n = 24)† or Glucose 30% 1 mL using a syringe followed by pacifier (n = 29) or Glucose 30% 1 mL using a syringe (n = 20)	Distress: Cry
Should breastfeeding and sweet-tasting solutions (sucrose, glucose) be combined together before vaccine injections (rather than breastfeeding or sweet-tasting solutions alone) in children 0-2 y?				
Sahebihagh 2011 (3,4),[35] Iran	DPT, hepatitis B vaccine IM; no injection details	N = 120; infants < 3 mo; between-groups design; multicenter, health centers	Breastfeeding based on infant's appetite before the procedure (n = 30) or Sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30) or Breastfeeding based on infant's appetite followed by sucrose 25% 2 min before the procedure (0.6 mL/kg) (n = 30) or Control (no intervention) (n = 30)†	Distress: NIPS, Cry
Should vapocoolants be applied before vaccine injections in children 0-3 y?				
Maikler 1991 (1,2),[75] USA	DPT 0.5 mL IM; 25-G, 5/8-inch needle; 90-degree angle; anterior thigh	N = 60; infants 6-30 wk; between-groups design; multicenter, pediatric ambulatory care and private clinics	Refrigerant topical anesthetic spray (dicholortetrafluorethane) for 2-3 s (n = 30)	Distress: MAX , Cry

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			or Control (compressed air spray) for 2-3 s (n = 30)	
Should vapocoolants be applied before vaccine injections in children > 3-17 y?				
Abbott 1995 (1,2),[76] Canada	DPT IM; no injection details	N = 90; children 4-5.5 y; between-groups design; multicenter, health clinics	Refrigerant topical anesthetic spray (Fluroethyl) on a sterile cotton ball held for 10 s (n = 30) or Placebo topical spray (compressed air with Freon) on a sterile cotton ball for 10 s (n = 30) or Control (no treatment) (n = 30)	Pain: VAS
Cohen 2009,[77] USA	DPTaP, Measles-Mumps-Rubella, and IPV IM; 25-G, 1-inch needle; thigh	N = 57; children 4-6 y; between-groups design; single center, primary pediatric care clinic	Vapocoolant (ethyl chloride) solution on a cotton ball applied for ~20 s (n = 31) or Control (standard care) (n = 26)	Pain: FPS-R, VAS
Cohen Reis 1997 (1),[41] USA	DTaP 0.5 mL IM; 26-G, ½-inch needle; 90-degree angle; deltoid	N = 62; children 4-6 y; between-groups design; single center, hospital primary care center	Lidocaine-prilocaine cream 5% 2.5 g for 60 min + distraction (blow on a pinwheel held by themselves or their parents) (n = 21)† or Vapocoolant (Fluorimethane) spray on a cotton ball applied for 15 s immediately before the procedure + distraction (n = 20) or Distraction alone (n = 21)	Pain: Bieri FPS, VAS
Eland 1981 (3,4),[78] USA	DPT 0.5 mL, IM; 25-G, 5/8-inch needle; vastus lateralis	N = 40; children 4.7-5.7 y; between-groups design; single center, pediatric clinic	Refrigerant topical anesthetic spray (Frigiderm) + cognitive information (n = 10) or Refrigerant topical anesthetic spray (Frigiderm) + no cognitive information (n = 10) or Aerosol air spray + cognitive information (n = 10) or Aerosol air spray + no cognitive information; spray applied 3-5 s on the leg before vaccination (n = 10)	Pain: VAS
Luthy 2013 (1),[79] USA	Vaccine NR; no injection details	N = 68; children 2-12 y; between-groups design; single center, pediatric office	Distraction (DVD before, during, and after the procedure) (n = 27)† or Vapocoolant spray for 3-7 s before the procedure (n = 18) or Control (no intervention) (n = 22)	VAS
Should vapocoolants be applied before vaccine injections in adults?				
Mawhorter 2004,[80] USA	Travel-specific vaccines IM or SC; no injection details	N = 185; adults > 18 y; between-groups design; single center, travel clinic	Vapocoolant (Fluorimethane) on a sterile cotton ball before the procedure (n = 93)	Pain: McGill PPI

(*Continued*)

TABLE 2. (*continued*)

First Author Year, Country	Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes*
			or Placebo (4°C, saline) on a sterile cotton ball before the procedure (n = 92)	
Should acetaminophen be given before vaccine injections in individuals of all ages?				
Hedén 2014,[81] Sweden	SC injection in implanted intravenous port	N = 51; children 1-18 y; between-groups design; single center, pediatric oncology center	Lidocaine-prilocaine patch/cream 5% ≥ 60 min + paracetamol (40 mg/kg crushed tablet in 5-10 mL of jam or yogurt) 60 min before procedure (n = 24) or Lidocaine-prilocaine patch/cream 5% ≥ 60 min + placebo (40 mg/kg crushed tablet in 5-10 mL of jam or yogurt) 60 min before procedure (n = 27)	Pain: VAS
Should ibuprofen be given before vaccine injections in individuals of all ages?				
Smith 1996,[82] Australia	VC; 20-G needle	N = 10; healthy volunteers; cross-over design; single center, hospital setting	Ibuprofen 5% cream 2 g 60 min before the procedure (n = 10) or Lidocaine-prilocaine cream 5% 2 g 60 min before the procedure (n = 10)	Pain: VAS

*Distress is the critical outcome in the absence of data for pain and/or fear in individuals incapable of self-report (eg, infants).

†Data not included in the analysis for that particular clinical question.

Studies were identified using the following notation: "First Author" "Year of Publication," "Country" [eg, Taddio 2014, Canada]. If studies contributed to multiple analyses, then "(#)" was added to enable their discernment [eg, Taddio 2014 (1)]. If the same author published > 1 study in the same year, then a lower case letter was added after the first article in the same year by the same author [eg, Taddio 2014a (1)].

Route: ID indicates intradermal; IM, intramuscular; SC, subcutaneous; VC, venous cannulation.

Outcomes: APS indicates Abbey Pain Scale; CAMPIS-R, Child-Adult Medical Procedure Interaction Scale-Revised; CFCS, Child Facial Coding System; CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; Cry, cry duration; DAN, Douleur Aiguë du Nouveau-né; FLACC, Face, Legs, Arms, Crying, Consolability; FPS, Faces Pain Scale; FPS-R, Faces Pain Scale-Revised; MAX, Maximally Discriminative Facial Movement Coding System; MBPS, Modified Behavioral Pain Scale; McGill PPI, McGill Present Pain Intensity; MFCS, Modified Neonatal Facial Coding Score; MNIPS, Modified Neonatal Infant Pain Scale; NFCS, Neonatal Facial Coding System; NIPS, Neonatal Infant Pain Scale; PAINAD, Pain Assessment in Advanced Dementia; PIPP, Premature Infant Pain Profile; UWCH Pain Scale, University of Wisconsin Children's Pain Scale; VAS, Visual Analog Scale.

Vaccines: DPT indicates diphtheria, pertussis, tetanus; DPTP, diphtheria, pertussis, tetanus, polio; DTaP, diphtheria, tetanus, acellular pertussis; DTaP-IPV-Hib, diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, *Haemophilus influenzae* type b; DTP, diphtheria, tetanus, pertussis; DTP-HBV-HIB, diphtheria, tetanus, pertussis-hepatitis B vaccine-*Haemophilus influenzae* type b; DTP-HIB, diphtheria, tetanus, pertussis-*Haemophilus influenzae* type b; DTP-HIB-IPV, diphtheria, tetanus toxoid, acellular pertussis, hepatitis B, inactivated polio vaccine; DTP-IPV-Hib, diphtheria, tetanus toxoid, acellular pertussis, inactivated polio vaccine, *Haemophilus influenzae* type b; HAV, hepatitis A vaccine; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; MCV, meningococcal C vaccine; MMR, Measles-Mumps-Rubella; PCV13, pneumococcal conjugate vaccine 13; wDPT, whole cell DPT.

NR indicates not reported.

majority of the studies included children, adolescents, or both (n = 52) and only 3 studies included adults.[51,80,82]

Quality of Included Studies and Risk of Bias

The methodologic quality (Risk of Bias) assessments for the critical outcomes of the included studies are presented in Table 3. Depending on the intervention evaluated, the overall Risk of Bias varied from high (eg, for breastfeeding and vapocoolants because of lack of blinding) to unclear (eg, for topical anesthetics and sweet-tasting solutions as there was insufficient information to make judgments) to low Risk of Bias (for acetaminophen based on a single study).

Overall Quality of Evidence and Treatment Effects

A quantitative summary of the treatment effects for available critical outcomes are described below. For several clinical questions, multiple indicators of the same critical outcome were included (eg, distress measured in the preprocedure phase of the procedure, the acute phase, or the recovery phase, or various combinations of these). For the purposes of presentation, the critical outcome indicators with the most number of participants are included. If the critical outcome was distress, the acute and the acute and recovery phases were also prioritized over other indicators of distress for presentation. Further, a qualitative summary across all critical outcomes is presented in Table 4. Information on immunogenicity (important outcome) is summarized in Table 5 while information on other important outcomes (adverse events, fidelity, feasibility, and preference) is presented in Table 6. Supporting GRADE Evidence Profiles and Summary of Findings tables (Tables, Supplemental Digital Content 1 to 14) and accompanying Forest plots (Figures, Supplemental Digital Content 1 to 14) for critically important and important outcomes are included as Supplemental Digital Content.

Breastfeeding

Should Breastfeeding be Used During Vaccine Injections in Children 0 to 2 Years?

The analgesic effect of breastfeeding was examined in 9 trials[22–27,29,30,33] including data on 858 infants (0 to 12 mo).

TABLE 3. Assessment of Risk of Bias of Included Trials for Critical Outcomes

First Author	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
Should breastfeeding be used during vaccine injections in children 0-2 y?								
Abdel Razek 2009[22]	No	No	No	Unclear	Yes	No	Yes	High
Dilli 2009 (1)[23]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Efe 2007[24]	Unclear	Unclear	No	Unclear	Yes	Yes	Unclear	High
Goswami 2013 (1)[25]	Yes	Yes	No	No	Yes	Yes	Yes	High
Iqbal 2014[26]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	High
Modarres 2013[27]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Shah Ali 2009[29]	No	No	No	No	Yes	Yes	Yes	High
Tavooni 2009[30]	No	No	No	No	Yes	Yes	Yes	High
Thomas 2011[33]	Unclear	Unclear	No	No	Yes	Yes	Unclear	High
If breastfeeding is not used during vaccine injections, should breastfeeding be used before vaccine injections in children 0-2 y?								
Achema 2011 (1)[34]	No	No	No	Unclear	Yes	Yes	Yes	High
Sahebihagh 2011 (1)[35]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Should topical anesthetics be applied before vaccine injections in children 0-12 y?								
Abuelkeir 2014[36]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Achema 2011 (2)[34]	No	No	No	Unclear	Yes	Yes	Yes	High
Basiri-Moghadam 2014[37]	No	Unclear	No	Yes	Yes	Yes	Yes	Unclear
Cassidy 2001[38]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Cohen 1999 (2)[39]	Unclear	Unclear	No	No	No	Unclear	Yes	High
Cohen 2006 (3,4)[40]	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	High
Cohen Reis 2007 (1)[41]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Dilli 2009 (2)[23]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Gupta 2013 (1)[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Halperin 2000[43]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Halperin 2002[44]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Kumar 2014[45]	Yes	No	Unclear	Unclear	Yes	Yes	Yes	High
O'Brien 2004 (thesis 2004)[46]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Taddio 1994[48]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Uhari 1993[49]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Should topical anesthetics be applied before vaccine injections in adolescents > 12 y and adults?								
Hansen 1993[50]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Taddio 1992[51]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Should topical anesthetics be used before vaccine injections in combination with breastfeeding during vaccine injections (rather than topical anesthetics or breastfeeding alone) in children 0-2 y?								
Gupta 2013 (2)[42]	Yes	Yes	No	No	Yes	Yes	Yes	High
Should sucrose solution be given before vaccine injections in children 0-2 y?								
Allen 1996 (1-12)[52]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear
Barr 1995[53]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Chattopadhyay 2011[54]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Dilli 2009 (3)[23]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Harrington 2012 (3,4)[55]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	High
Harrison 2014 (1,2)[56]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Hatfield 2008[57]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Hatfield 2008a[58]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Lewindon 1998[60]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Liaw 2011 (2)[61]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear

(*Continued*)

TABLE 3. (*continued*)

First Author	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
Moradi 2012 (1,2)[62]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Mowrey 2008[64]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Poulsen 2009[65]	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	High
Priambodo 2008[66]	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Ramenghi 2002 (1,2)[67]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Sahebihagh 2011 (4)[35]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Soraino Faura 2003[68]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Yilmaz 2014 (1,2)[69]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Should glucose solution be given before vaccine injections in children 0-2 y?								
Chermont 2009 (4)[70]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Golestan 2007 (1,2)[71]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Goswami 2013 (2)[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Kassab 2012[72]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Mörelius 2009 (1,4)[73]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Thyr 2007[74]	Unclear	Unclear	No	Yes	Yes	Yes	Unclear	High
Should sweet-tasting solutions (sucrose, glucose) be used before vaccine injections in combination with non-nutritive sucking (finger/thumb, pacifier) during vaccine injections (rather than sweet-tasting solutions or non-nutritive sucking alone) in children 0-2 y?								
Mörelius 2009 (3,4)[73]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Should breastfeeding and sweet-tasting solutions (sucrose, glucose) be combined together before vaccine injections (rather than breastfeeding or sweet-tasting solutions alone) in children 0-2 y?								
Sahebihagh 2011 (3,4)[35]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Should vapocoolants be applied before vaccine injections in children 0-3 y?								
Maikler 1991 (1,2)[75]	Yes	Unclear	No	Yes	Yes	Yes	Unclear	High
Should vapocoolants be applied before vaccine injections in children > 3-17 y?								
Abbott 1995 (1,2)[76]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Cohen 2009[77]	Unclear	No	No	No	Yes	Yes	Yes	High
Cohen Reis 2007 (1)[41]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Eland 1981 (3,4)[78]	Unclear	Unclear	No	No	Yes	Yes	Unclear	High
Luthy 2013 (1)[79]	Yes	Unclear	No	No	Yes	Yes	Unclear	High
Should vapocoolants be applied before vaccine injections in adults?								
Mawhorter 2004[80]	Yes	Unclear	No	Yes	Yes	No	Unclear	High
Should acetaminophen be given before vaccine injections in individuals of all ages?								
Hedén 2014[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Should ibuprofen be given before vaccine injections in individuals of all ages?								
Smith 1996[82]	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear

Studies were identified using the following notation: "First Author" "Year of Publication" [eg, Taddio 2014]. If studies contributed to multiple analyses, then "(#)" was added to enable their discernment [eg, Taddio 2014 (1)]. If the same author published > 1 study in the same year, then a lower case letter was added after the first article in the same year by the same author [eg, Taddio 2014a (1)].

In all studies, breastfeeding was commenced immediately before vaccination and continued during and afterward. In the included trials, the comparator arm varied from the infant being swaddled in the bassinet/placed on the table[24,26] held in the mother's arms,[27,29] restrained by the mother,[22] given distilled water[25] to a no intervention roup.[23,30,33]

Benefit of breastfeeding was observed for all the critical outcomes analyzed, including acute and acute plus recovery distress (Table and Figure, Supplemental Digital Content 1, http://links.lww.com/CJP/A249). The SMD was −1.78 (CI, −2.35, −1.22) for acute distress (n = 792; data from 8 studies).[22,23,25–27,29,30,33] For distress during the

TABLE 4. Summary of Results for Critically Important Outcomes

Clinical Questions	Critical Outcomes*	Benefit of Intervention†	Quality of Evidence‡
Pharmacological interventions			
Should breastfeeding be used during vaccine injections in children 0-2 y?	Distress	Yes	Very low
If breastfeeding is not used during vaccine injections, should breastfeeding be used before vaccine injections in children 0-2 y?	Distress	Mixed	Low
Should topical anesthetics be applied before vaccine injections in children 0-12 y?	Pain, distress, fear	Mixed	Very low
Should topical anesthetics be applied before vaccine injections in adolescents > 12 y and adults?	Pain	Yes	Moderate
Should topical anesthetics be used before vaccine injections in combination with breastfeeding during vaccine injections (rather than topical anesthetics or breastfeeding alone) in children 0-2 y?	Distress	Mixed	Low
Should sucrose solution be given before vaccine injections in children 0-2 y?	Distress	Yes	Moderate
Should glucose solution be given before vaccine injections in children 0-2 y?	Distress	Mixed	Moderate
Should sweet-tasting solutions (sucrose, glucose) be used before vaccine injections in combination with non-nutritive sucking (finger/thumb, pacifier) during vaccine injections (rather than sweet-tasting solutions or non-nutritive sucking alone) in children 0-2 y?	Distress	Mixed	Very low
Should breastfeeding and sweet-tasting solutions (sucrose, glucose) be combined together before vaccine injections (rather than breastfeeding or sweet-tasting solutions alone) in children 0-2 y?	Distress	No	Low
Should vapocoolants be applied before vaccine injections in children 0-3 y?	Distress	No	Low
Should vapocoolants be applied before vaccine injections in children > 3-17 y?	Pain	No	Low
Should vapocoolants be applied before vaccine injections in adults?	Pain	Mixed	Low
Should acetaminophen be given before vaccine injections in individuals of all ages?	Pain, distress	No	Low
Should ibuprofen be given before vaccine injections in individuals of all ages?	Pain, distress	No	Very low

*Includes results for the critical outcomes that were evaluated in included studies only.

†The results for the effect of the intervention have been summarized across all evaluated critical outcomes, and are expressed using the following notation: Yes = benefit was observed across all evaluated critical outcomes; Mixed = benefit was observed for ≥1 but not all evaluated critical outcomes; No = no evidence of benefit was observed for any of the evaluated critical outcomes.

‡Reflects the lowest quality of evidence rating across all evaluated critical outcomes, whereby rankings range from High to Moderate to Low to Very low. Distress is the critical outcome in the absence of data for pain and/or, fear, or both in individuals who cannot verbalize (eg, infants).

acute plus recovery phase (n = 424) the SMD was −1.89 (CI, −3.19, −0.59). Considerable heterogeneity was reported for this outcome, which can be explained by the potential differences in the implementation of the intervention (breastfeeding and the control group) and age of the infant (studies included infants less than 24 h of age to up to 12 mo). There was low to very low quality of evidence due to methodologic limitations of the included studies (Table, Supplemental Digital Content 2, http://links.lww.com/CJP/A250).

If Breastfeeding is Not Used During Vaccine Injections, Should Breastfeeding be Used Before Vaccine Injections in Children 0 to 2 Years?

Two trials[34,35] including 100 infants (6 wk to less than 3 mo of age) evaluated the effect of breastfeeding before vaccination. Breastfeeding ceased 2 to 60 minutes before injection.[34,35] The control group included holding[34] or no intervention.[35] The results were mixed (Table and Figure, Supplemental Digital Content 3, http://links.lww.com/CJP/A251). Breastfeeding prevaccine injection was associated with lower acute distress: SMD −1.43 (CI, −2.14, −0.72) as well as acute plus recovery distress combined: SMD −1.47 (CI, −2.05, −0.90) (Figure, Supplemental Digital Content 4, http://links.lww.com/CJP/A252). No benefit was noted for distress recovery. The quality of evidence ranged from moderate to low quality (Table, Supplemental Digital Content 5, http://links.lww.com/CJP/A253).

Topical Anesthetics

Should Topical Anesthetics be Applied Before Vaccine Injections in Children 0 to 12 Years?

Fifteen studies[23,34,36–46,48,49] including infants and children investigated the effect of topical anesthetics. In 10 included studies, vaccines were administered intramuscularly[34,37–39,41,42,44,45,48,49]; in 2 studies,[43,46] they were

TABLE 5. Impact of Topical Anesthetics and Acetaminophen on Immune Response to Vaccines*

	Lidocaine-Prilocaine 5% Patch[43,44]		Amethocaine Gel 4%[46]		Acetaminophen[84–88]	
Vaccines†	Seroconversion Rate	GMCs of Antibody Titer	Seroconversion Rate	GMCs of Antibody Titer	Seroconversion Rate	GMCs of Antibody Titer
DPTaP-IPV-Hib						
Diphtheria	No effect	No effect	NA‡	NA	NA	Reduced
Tetanus	No effect	No effect	NA	NA	NA	Reduced
Pertussis	No effect	No effect	NA	NA	NA	Reduced
Polio virus (1, 2, and 3)	No effect	No effect	NA	NA	No effect	No effect
Haemophilus influenzae type b	No effect	No effect	NA	NA	NA	Reduced
Hepatitis B	No effect	No effect	NA	NA	No effect	Reduced
Human rotavirus	NA	NA	NA	NA	No effect	No effect
Influenza	NA	NA	NA	NA	No effect	No effect
Mumps-Measles-Rubella						
Mumps	No effect	No effect	No effect	No effect	NA	NA
Measles	No effect	No effect	No effect	No effect	NA	NA
Rubella	No effect	No effect	No effect	No effect	NA	NA
PHiD-CV	NA	NA	NA	NA	NA	Reduced

*Data on adverse events for topical anesthetics and oral analgesics are reported in Table 6.

†DPTaP-IPV-Hib = Diphtheria-Tetanus-acellular Pertussis-inactivated Poliovirus-*Hemophilus influenzae* type b; DTPa + HBV + IPV/Hib = Diphtheria-teatnus-3 component acellular pertussis-hepatitis B-inactivated poliovirus type 1, 2 and 3-*Hemophilus influenzae* type; GMCs = Geometric mean concentrations; HRV = Human rotavirus vaccine; PHiD-CV = Pneumococcal nontypeable *Haemophilus influenzae* protein D-conjugate vaccine; MMR = Measles-Mumps-Rubella

‡NA: no data available; No effect = rate of seroconversion similar in topical anesthetic and placebo group; Reduced = reduction in the GMCs antibody titers.

administered subcutaneously; and in 3 studies,[23,36,40] both intramuscular (IM) and SC vaccines were given. Lidocaine-prilocaine cream 5% was applied in 11 studies,[23,34,36,37,39–42,44,47,48] lidocaine-prilocaine patch 5% was applied in 3 studies,[38,43,44] whereas amethocaine gel 4% was applied in 1 study.[46] The majority of studies (n = 8) included a placebo.[36,38,41–43,45,47,48] A meta-analysis of 13 studies[23,34,36–39,42–46,48,49] including 1424 infants demonstrated lower levels of acute distress in the topical anesthetics group: SMD −0.91 (CI, −1.36, −0.47). Observer-rated acute distress for child was lower in the topical anesthetics group: SMD −1.13 (CI, −1.78, −0.47) in 1 study including 42 children.[41] For distress during the acute plus recovery phase (n = 546) the SMD was −0.68 (CI, −1.24, −0.13). The results were mixed for other indicators of distress. A meta-analysis of 3 studies[38,39,41] including 269 children between 4 and 11 years showed no benefit of topical anesthetics on self-report of pain: SMD −0.29 (CI, −0.64, 0.05). However, removal of the data from 1 study with a high Risk of Bias[39] altered the result in favor of topical anesthetics: SMD −0.47 (CI, −0.73, −0.21). The SMD (CI) for fear was 0.04 (CI, −0.29, 0.37; n = 68) (Table and Figure, Supplemental Digital Content 6, http://links.lww.com/CJP/A254). The quality of evidence ranged from moderate to very low (Table, Supplemental Digital Content 7, http://links.lww.com/CJP/A255).

Should Topical Anesthetics be Applied Before Vaccine Injections in Adolescents Older than 12 Years and Adults?

Two studies[50,51] evaluated the analgesic effects of topical anesthetics in adolescents older than 12 years and adults. Pain was lower in the topical anesthetic group: SMD −0.85 (CI, −1.38, −0.32) in the study by Taddio et al,[51] whereas acute distress was not lower: SMD 0.05 (CI, −0.31, 0.41) in the study by Hansen et al[50] (Table and Figure, Supplemental Digital Content 8, http://links.lww.com/CJP/A256). The quality of evidence was moderate (Table, Supplemental Digital Content 9, http://links.lww.com/CJP/A257).

Immunogenicity

Three trials,[43,44,46] including 445 infants and children assessed antibody response following vaccination. Results are presented in Table 5. There was no difference in the immune response to vaccine in topical anesthetics compared with placebo group for Measles-Mumps-Rubella, diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b, and hepatitis B. In a separate study, Dohlwitz et al[83] reported no effect of topical anesthetics on Bacillus-Calmette-Guérin vaccine response in 388 children.

Should Topical Anesthetics be Used Before Vaccine Injections in Combination With Breastfeeding During Vaccine Injections (Rather than Topical Anesthetics or Breastfeeding Alone) in Children 0 to 2 Years?

In one study[42] including 60 infants less than 3 months of age, topical anesthetics combined with breastfeeding were compared with topical anesthetics alone during vaccine injections. Distress was the critical outcome. The results were mixed (Table and Figure, Supplemental Digital Content 10, http://links.lww.com/CJP/A258). The combination of topical anesthetics preinjection and breastfeeding during injection did not reduce distress in the acute phase of the procedure (SMD: −0.35 [CI, −0.86, 0.16]); however, distress during the acute plus recovery phase of the procedure was reduced (SMD: −0.83 [CI, −1.36, −0.30]) (Figure, Supplemental Digital Content 11, http://

TABLE 6. Summary of the Impact of Interventions on Adverse Events,* Fidelity, Feasibility, and Willingness to Use and Pay

	Outcomes			
Interventions	**Adverse Events†**	**Fidelity/Correct Use of Intervention**	**Feasibility**	**Willingness to Use and/or Pay**
Breastfeeding	Incidence of aspiration, vomiting, cyanosis, and respiratory change[22,24]: Breastfeeding group: 0% (n = 93) Control group: 0% (n = 93)	Infant acceptance to breastfeed[23]: 95% (n = 77)	NA	NA
Topical anesthetics	Pallor[36,38,43,44,46,51]: Topical anesthetic group: 42% (n = 442) Placebo group: 18% (n = 439) Erythema[36,38,43,44,46,51]: Topical anesthetic group: 29% (n = 442) Placebo group: 20% (n = 439)	Parent correct application[38,48]: 96% (n = 261)	Feasibility for inclusion in parent schedule[48]: 88% (n = 96) Ease of application for parent[48]: 91% (n = 96)	Children willingness to use[39]: 33% (n = 34) Families/parents willingness to use[49,50]: 65% (n = 272) Parents willing to pay $11.90 cents for lidocaine-prilocaine cream for future injections (n = 41)[41]
Sweet-tasting solutions (sucrose)	Cough, gagging, or choking episodes[58,60,64]: Sucrose group: 3.4% (n = 119) Water group: 0.8%	NA	NA	Parents willingness to use intervention[56]: 93% (n = 29) (sucrose or water)
Sweet-tasting solutions (glucose)	Nausea, vomiting, or physiological instability[70]: Glucose group: 0% (n = 160) Control group: 0% (n = 160)	NA	NA	NA
Vapocoolants	Sting at the application site[41,79,80]: Vapocoolant group: 0.7% (n = 142) (child had eczema) Control group: 0% (n = 92)	NA	NA	Parents would use vapocoolants in future[41,79]: 82% (n = 38) Parents willingness to pay: $8.40 (n = 41)[41]
Oral analgesics (acetaminophen)	Nausea[81]: Acetaminophen group: 0% (n = 24) Placebo group: 2% (n = 27)	NA	NA	NA

*Data on immunogenicity for topical anesthetics and oral analgesics are presented in Table 5.
†Reported as percentages; n = number of participants contributing to the data.
NA indicates not applicable.

links.lww.com/CJP/A259). The quality of evidence was low (Table, Supplemental Digital Content 12, http://links.lww.com/CJP/A260).

Sweet-tasting Solutions

Should Sucrose Solution be Given Before Vaccine Injections in Children 0 to 2 Years?

Eighteen studies including infants and young children aged 2 weeks to 48 months investigated the effects of sucrose.[23,35,52–58,60–62,64–69] The concentration of sucrose ranged from 12% to 75% except for the study by Chattopadhyay et al[54] where the concentration of sucrose was described as a "saturated solution." The majority of studies (n = 9) used sucrose in the concentration of 20% to 33%.[35,55–58,61,62,67,69] Except for 3 studies,[52,57,58] all used a volume of 2 mL. The majority of studies (n = 15) administered sucrose 2 minutes before the procedure.[23,35,52,53,55–58,61,62,64–67,69]

In a meta-analysis including 881 infants, sucrose was associated with lower acute distress: SMD −0.37 (CI, −0.67, −0.06). Similarly, acute plus recovery distress score was lower in the sucrose group: SMD −0.76 (CI, −1.19, −0.34); n = 2071 (Table and Figure, Supplemental Digital Content 13, http://links.lww.com/CJP/A261). The RR (CI) for dichotomous outcome of acute distress was 0.37 (CI, 0.2-0.69) (Figure, Supplemental Digital Content 14, http://links.lww.com/CJP/A262). The quality of evidence of included studies was high to moderate (Table, Supplemental Digital Content 15, http://links.lww.com/CJP/A263).

Subgroup Analysis

Benefit of sucrose in the concentration of 50% or 70% was observed for all the critical outcomes analyzed, including acute distress and acute plus recovery distress. The SMD (CI) were −0.31 (−0.61, −0.02; n = 259 infants) for acute distress; and −1.43 (−2.34, −0.52; n = 1006 infants) for acute plus recovery distress. Mixed results were found for sucrose in the concentration of 20% to 33%. Benefit was observed for the acute plus recovery (SMD −0.85 [CI, −1.6, −0.11]) and recovery phases (SMD −1.13 [CI: −1.89, −0.37]). There was no evidence of a benefit of sucrose in the concentration of 12% across all indicators of distress analyzed (Table and Figure, Supplemental Digital Content 13, http://links.lww.com/CJP/A261).

Should Glucose Solution be Given Before Vaccine Injections in Children 0 to 2 Years?

Six trials[25,70–74] investigated the effect of glucose on vaccine injection pain in infants 12 hours to 12 months. The concentration of glucose was 25% in 3 studies,[25,70,72] 30% in 2 studies,[73,74] and 50% in 1 study.[71] The volume administered ranged from 1 to 2 mL and timing varied from 2 minutes before to immediately prior the procedure. The results were mixed (Table and Figure, Supplemental Digital Content 16, http://links.lww.com/CJP/A264). In a meta-analysis including all trials (n = 818 infants), acute plus recovery distress was lower in the glucose group: SMD −0.69 (CI, −1.03, −0.35). There was no evidence of a benefit of glucose on acute distress (n = 520): SMD −0.59 (CI, −1.38, 0.20) (Table and Figure, Supplemental Digital Content 16, http://links.lww.com/CJP/A264). The quality of evidence ranged from high to moderate (Table, Supplemental Digital Content 17, http://links.lww.com/CJP/A265).

Should Sweet-tasting Solutions (Sucrose, Glucose) be Used Before Vaccine Injections in Combination With Non-Nutritive Sucking (Finger/Thumb, Pacifier) During Vaccine Injections (Rather than Sweet-tasting Solutions or Non-Nutritive Sucking Alone) in Children 0 to 2 Years?

One study[73] including 74 infants 3 months of age compared the effect of sweet-tasting solutions (glucose) before vaccine injection and non-nutritive sucking during vaccine injection to sweet-tasting solution or non-nutritive sucking alone. There was no evidence of benefit of the combination of glucose and non-nutritive sucking (pacifier) compared with glucose or non-nutritive sucking (pacifier) alone across all indicators of distress evaluated. For acute plus recovery, the SMD was −0.32 (CI, −0.79, 0.15) and the RR was 0.99 (CI, 0.78, 1.26) (Table and Figure, Supplemental Digital Content 18, http://links.lww.com/CJP/A266). The included study did not assess treatment fidelity with non-nutritive sucking. The quality of evidence was very low (Table, Supplemental Digital Content 19, http://links.lww.com/CJP/A267).

Should Breastfeeding and Sweet-tasting Solutions (Sucrose, Glucose) be Combined Together Before Vaccine Injections (Rather than Breastfeeding or Sweet-tasting Solutions Alone) in Children 0 to 2 Years?

One study[35] including 90 infants aged less than 3 months evaluated the effect of a combination of breastfeeding and sweet-tasting solutions (sucrose) versus breastfeeding or sucrose alone. There was no evidence of a benefit of breastfeeding and sucrose versus either alone across all indicators of distress, The SMD for acute distress was 0.28 (CI, −0.34, 0.90) and for acute recovery it was 0.06 (CI, −0.37, 0.5) (Table and Figure, Supplemental Digital Content 20, http://links.lww.com/CJP/A268). The quality of evidence was low (Table, Supplemental Digital Content 21, http://links.lww.com/CJP/A269).

Vapocoolants

Should Vapocoolants be Applied Before Vaccine Injections in Children 0 to 3 Years?

One study[75] including 60 infants between 6 weeks and 3 months investigated the effect of vapocoolant versus control (compressed air spray). In this study, the vapocoolant and placebo were both sprayed on the injection site for 2 to 3 seconds right before injection. Vapocoolant spray did not reduce acute distress (the only indicator of distress included in the study): SMD −0.44 (CI, −0.96, 0.07) (Table and Figure, Supplemental Digital Content 22, http://links.lww.com/CJP/A270). The quality of evidence was low (Table, Supplemental Digital Content 23, http://links.lww.com/CJP/A271).

Should Vapocoolants be Applied Before Vaccine Injections in Children Older than 3 to 17 Years?

Five trials were included in the systematic review.[41,76–79] In 3 trials,[41,76,77] the vapocoolant was applied to the injection site using sterile cotton ball for 10 to 20 seconds, whereas in the other 2 trials, the vapocoolant was sprayed directly on the site with application time of 3 to 7 seconds.[78,79] The control group consisted of placebo spray, distraction, or a no intervention group. In a meta-analysis of 4 trials including 228 children, there was no evidence of a benefit on pain: SMD −0.38 (CI, −0.89, 0.13) (Table and Figure, Supplemental Digital Content 24, http://links.lww.com/CJP/A272). The quality of evidence was low (Table, Supplemental Digital Content 25, http://links.lww.com/CJP/A273).

Should Vapocoolants be Applied Before Vaccine Injections in Adults?

One trial[80] including 185 adults was identified for inclusion in the review. A cotton ball saturated with vapocoolant or cold saline (4°C) was applied for 15 seconds in the arm. Acute pain was lower in the vapocoolant group: SMD −0.78 (CI, −1.08, −0.48) (Table and Figure, Supplemental Digital Content 26, http://links.lww.com/CJP/A274). The quality of evidence was low (Table, Supplemental Digital Content 27, http://links.lww.com/CJP/A275).

Oral Analgesics

Should (Oral) Acetaminophen be Given Before Vaccine Injections in Individuals of all Ages?

No trial evaluating the effectiveness of orally administered acetaminophen for vaccine injection pain was identified, and indirect evidence was obtained from the closest related needle procedure (SC injection into an implanted intravenous port).[81] The study population included 51 infants and children (1 to 18 y of age) with cancer randomized to acetaminophen or placebo 60 minutes before the procedure. All children in both the groups also received lidocaine-prilocaine patch/cream. There was no difference in pain between groups: SMD −0.64 (CI, −1.43, 0.15) (Table and Figure, Supplemental Digital Content 28, http://links.lww.com/CJP/A276). The quality of evidence was low (Table, Supplemental Digital Content 29, http://links.lww.com/CJP/A277).

Immunogenicity

Five studies[84–88] evaluated the effect of prophylactic acetaminophen/paracetamol (administered at the time or just after the vaccine) on immune response to vaccination. Results from these studies are presented in Table 5. In 3 trials including 442 adults, the use of prophylactic acetaminophen did not affect the immune response to influenza vaccine as measured using the hemagglutination inhibition antibody assay.[84,85,87]

In the study by Doedée et al,[86] use of prophylactic paracetamol was associated with a 26% reduction in anti-hepatitis B surface antigen antibody levels in 178 adults even though all participants achieved levels of >10.0 IU/L (considered to be seroprotective). Prophylactic paracetamol was associated with reduction in immune response to DTPa + HBV + IPV/Hib (hexavalent diphtheria-tetanus-3 component acellular pertussis-hepatitis B-inactivated poliovirus type 1, 2, and 3-*Haemophilus influenzae* type b); and PHiD-CV (10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D-conjugate vaccine) in 459 children.[88]

Should (Oral) Ibuprofen be Given Before Vaccine Injections in Individuals of all Ages?

No trial was identified that evaluated orally administered ibuprofen for vaccine injection pain, and evidence was obtained from a cross-over trial that compared the effectiveness of ibuprofen 5% cream to lidocaine-prilocaine 5% cream in 20 adults undergoing venipuncture.[82] Lidocaine-prilocaine 5% cream was superior to ibuprofen cream in preventing the pain associated with venipuncture: SMD 0.77 (CI, 0.06, 1.48) (Table and Figure, Supplemental Digital Content 30, http://links.lww.com/CJP/A278). The quality of evidence was very low (Table, Supplemental Digital Content 31, http://links.lww.com/CJP/A279).

Immunogenicity

No studies have evaluated the effect of oral ibuprofen on immune response to vaccines.

DISCUSSION

In this systematic review and meta-analysis, we examined the effectiveness of various pharmacological interventions and combined interventions for vaccine injection pain in individuals across the lifespan. These interventions included breastfeeding during and before vaccine injection, topical anesthetics, sweet-tasting solutions (sucrose and glucose), vapocoolants, oral analgesics (acetaminophen and ibuprofen), and the combination of 2 interventions versus 1 intervention. We found evidence for a benefit of breastfeeding, topical anesthetics, sweet-tasting solutions, and combinations of topical anesthetics and breastfeeding for reducing vaccine injection pain in infants and children. In adults, limited data demonstrate some benefit of topical anesthetics and vapocoolants.

Breastfeeding

This review found evidence of a benefit of breastfeeding. These findings are consistent with those reported in our previous review and clinical practice guideline[6,8] and a Cochrane review including neonates undergoing needle procedures.[89] Breastfeeding is a simple and cost-neutral intervention that can be easily adopted across vaccination settings by caregivers and health care professionals. It provides analgesia through several mechanisms including comfort (close proximity to the mother), distraction, and stimulation of the orotactile and mechnoreceptors (sucking on the breast),[90] and presence of sweet-tasting substances in the mother's milk.[91–93] Exclusive breastfeeding until 6 months is recommended by the World Health Organization due to the nutritional and psychological benefits of breastfeeding; and supports breastfeeding for 2 years or beyond.[94] The analgesic effects of breastfeeding further promote breastfeeding as the method of choice for infant feeding.

For the intervention to be effective, an adequate latch should be established before and continued during and after the procedure. This may not be always possible to achieve as the infant may be sleepy or not interested in feeding or not hungry and an alternative pain management strategy should be considered.

Breastfeeding Prevaccine Injection

If breastfeeding cannot be achieved during the procedure, breastfeeding prevaccine injection should be encouraged as it has some benefits on distress secondary to satiation of the infant.[34,35] There are no data regarding breastfeeding before and during vaccine injections. It is possible that breastfeeding before may cause less infants to latch during the vaccine injections.

Topical Anesthetics

Topical anesthetics were effective in reducing pain associated with vaccine injections administered by various routes including intramuscular and subcutaneous in children and adults. This conclusion was based on 17 studies which predominantly used a comparator of placebo. In terms of mechanism, topical anesthetics temporarily inhibit the generation and transmission of pain impulses by blocking the action potentials across nerve endings located in the dermis.[95] By producing dermal analgesia (topical local anesthetics penetrate to a depth of ~5 mm below the skin surface), they effectively reduce the pain from needle puncture.

Despite their proven effectiveness, topical anesthetics are not used in clinical practice as part of standard care. Topical anesthetics require an application time of 20 to 60 minutes depending on the commercial preparation that is used. This is an obstacle to clinical use. However, if there is insufficient waiting time at the clinic, they can be applied ahead of time. In 2 studies included in this review,[38,48] instructions were provided to parents on how to apply the cream at home on the day of vaccination. In the study by Cassidy et al,[38] 54/161 (86%) of the parents applied the topical anesthetic correctly and in the study by Taddio et al,[48] 96/100 (96%) of the parents applied it correctly. Further, 84/96 (88%) parents reported that they could fit the application of the cream in their schedules and 87 (91%) reported that the cream was not difficult to apply.[48] Our findings regarding the feasibility of home application is consistent with other studies in which topical anesthetics have been applied at home by parents before venipuncture required for minor day care surgeries (eg, endoscopy) provided optimal education was given.[96,97] Two studies reported on the mean waiting time before vaccine injection in the clinics demonstrating feasibility of application of topical anesthetics onsite. In the study by Abuelkheir et al[36] (Saudi Arabia), the mean waiting time before the vaccine injection was 57 minutes (SD = 16.7), whereas in the study by Taddio et al[98] (Canada), the mean waiting time reported was 41.6 minutes (SD = 28.6). Application of the topical anesthetics while awaiting the appointment is possible if there is sufficient time. This also allows clinicians to assist in their administration (eg, ensuring they are placed in the correct anatomic location).

The cost of topical anesthetics requires some discussion. The cost of EMLA patch is ~Canadian $12, while the cost of a 60 g tube is ~$50 which can be used for

multiple applications. At present, individuals are usually asked to absorb their cost. It is generally assumed that individuals would not pay, however, there are some data suggesting they would. In 1 included study, parents were willing to pay $11.90 for topical anesthetics for future injections.[41] In another study by Ughasoro et al[99] caregivers were willing to pay $8.31 for topical anesthetics which is more that the cost of the cream itself.

Several practical issues should be addressed before its adoption in clinical practice including: (1) ease of availability over the counter depending on geographic location (eg, in USA topical anesthetics are available only if prescribed); (2) time to apply the topical anesthetics while waiting for injection to be administered (wait times vary between clinics); and (3) feasibility of parental education. Therefore, helping parents plan for and advocate for proper pain management ahead of time (eg, prescriptions for topical anesthetics when availability in some geographical regions is limited and educating parents), is critical for its implementation in practice.

There is concern that concomitant use of topical anesthetics during vaccination may lead to inactivation of the vaccines or impair absorption due to its antimicrobial activity.[100–103] No interference by topical local anesthetics were detected with the DPTaP-IPV-Hib, hepatitis B, or Measles-Mumps-Rubella vaccines in any of the trials that were included in this review (Table 5).[43,44,46] The data are consistent with studies performed in adults undergoing Bacille-Calmette-Guérin vaccine administration.[83] It is not clear whether these results with topical anesthetics can be generalized to other vaccine antigens; we suggest that testing for interactions between topical local anesthetics should be incorporated in trials evaluating new vaccine antigens.

The use of topical anesthetics was associated with transient local skin reactions such as pallor and erythema.

Sweet-tasting Solutions

We found sufficient evidence of benefit from sucrose to reduce pain response during vaccination.[23,35,52–58,60–62,64–69] The majority of studies used sucrose in the concentration of 20% to 33% with a typical volume of 2 mL.[35,55–58,61,62,67,69] The sucrose concentrations used ranged from 12% to 75%. Also sucrose was administered 2 minutes before the procedure in majority of the studies.[23,35,52,53,55–58,61,62,64–67,69]

Our finding of a beneficial effect of sucrose for vaccine injection pain is consistent with results of studies involving other invasive skin-breaking procedures performed in neonates and young infants such as heel lance and venipuncture.[104] The mechanism of action of sucrose is believed to include release of endogenous opioids and distraction.[105]

A subgroup analysis based on the concentration of sucrose demonstrated a consistent benefit of concentrations of 50% or 75% across all indicators of infant distress, whereas the results were mixed with concentrations between 20% and 33%. Sucrose in the concentration of 12% was not effective in reducing any of the distress indicators. On the basis of this analysis, sucrose in the dose of 2 mL with concentrations >20% should be used for vaccine injection pain.

Adverse events from sweet-tasting solutions such as coughing and gagging were reported in only 1 trial,[58] whereas no episodes of choking or any other adverse events were reported in 2 other trials.[60,64] None of these adverse events were clinically significant, as all infants recovered spontaneously within 10 seconds. More consistent documentation of the presence or absence of adverse events is recommended in future research.

The effectiveness of glucose was mixed and not as robust as sucrose. Sucrose should be the preferred sweet-tasting solution, however, if not available glucose should be considered as an alternative. Glucose solution for intravenous administration is easily available in clinical practice in resource-limited countries and is a practical alternative to sucrose for pain management. In settings where sweet-tasting solutions are not available, they can be prepared by using 1 packet of table sugar mixed with 2 teaspoonfuls of clean/sterile water; however, attention needs to be paid to the use of clean/sterile water.

Vapocoolants

Vapocoolants are volatile liquids that when applied on the skin provides transient anesthesia secondary to evaporation-induced skin cooling.[106] The cold sensation may reduce pain by gating pain signals so that cold is experienced rather than pain. The other proposed mechanism is that they decrease the velocity of nerve impulse transmission across nerve fibers.[107] As vapocoolants cause cooling and/or burning sensations on the skin, it can be uncomfortable for some individuals including children who may perceive it as a noxious stimulus.[8]

On the basis of the lack of evidence of benefit, vapocoolants cannot be recommended for use in infants and children. In a single study in adult population, vapocoolants were effective in reducing pain associated with vaccine injection.[80] Vapocoolants are an attractive alternative to topical anesthetics due to the short application time (s). However, their application may be associated with discomfort because of the cold sensation that may be perceived as painful. In the included study, there was no report of discomfort from vapocoolant application. In a recent systematic review on venipuncture pain, the pain relief provided by vapocoolants was offset by the pain of their application.[108] As the cold sensation may be perceived differently among individuals, their preferences should be taken into consideration when offering vapocoolants.

Oral Analgesics

No trials that evaluated oral analgesics (acetaminophen or ibuprofen) for vaccination pain were identified. Evidence from other needle procedures showed no benefit of either acetaminophen or ibuprofen.[81,82] More concerning is the recent data on the effect of prophylactic acetaminophen on immune response study to vaccination.[86,88] The use of prophylactic paracetamol was associated with reduction in antibody levels for several vaccines evaluated including hepatitis B, DTPa + HBV + IPV/Hib, and PHiD-CV.[86,88] No data on the effect of prophylactic ibuprofen on immune response was identified. Oral analgesics contain sweet-tasting solutions as flavoring agents and individuals may wish to offer them for use before vaccinations; however, sweet-tasting solutions such as sucrose and glucose should be offered instead because of the potential to interfere with the vaccine response.

Two Versus One Intervention

There was evidence of a benefit of the combination of topical anesthetics and breastfeeding.[42] There were no additive benefits of combining glucose and pacifier[73] or breastfeeding and sucrose.[35] These data are limited to single

studies with small sample sizes. In previous studies in neonates, the combination of sucrose and pacifiers has been shown to work better than either alone.[109]

Strengths, Limitations, and Future Research

The major strength of this review is the availability of large evidence base for some of the included interventions (eg, breastfeeding, topical anesthetics in children, and sweet-tasting solutions) and methodological rigor in terms of blinding and quality of included studies. This results in more confidence in our conclusions. In addition, a meticulous approach that included both the GRADE and Cochrane methodologies was used to conduct this systematic review and meta-analysis.

Methodologic challenges and limitations of this review include the small sample sizes for some of the included interventions (eg, vapocoolants across lifespan, topical anesthetics in adults, and oral analgesics) and limited age range of the participants. Furthermore, many of these trials were published before the Consolidated Standards of Reporting Trials (CONSORT) guidelines[110] were adopted. On the basis of our review, areas for future research include: (1) evaluation of the effectiveness of expressed breast milk and bottle feeding (in babies whose parents choose to offer bottle to provide expressed breast milk or formula); (2) evaluation of the effects of topical anesthetics on immune response to newer vaccines across lifespan; (3) studies to identify the optimal dose, concentration, and timing of administration of sweet-tasting solutions; (4) additional studies on vapocoolants to confirm or refute its use in children and adults; and (5) combined interventions compared with single active intervention with the goal to reduce pain experienced to zero.

In summary, breastfeeding, topical anesthetics, and sweet-tasting solutions are effective interventions that can be used in infants, children, and adults to reduce vaccine injection pain. Despite the evidence regarding the effectiveness of these interventions for >20 years, children and adults around the world have not reaped the benefits. Rather than conducting effectiveness/efficacy studies for well-studied, effective interventions, it is time to conduct implementation science research so that the use of these interventions becomes the standard of care in clinical practice globally. Educating our consumers (children, parents, and adults undergoing vaccination) and health care providers is crucial to make these changes. There is some evidence that education of individuals can lead to increased use.[111]

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