HELPinKids&Adults 2.0 (expanded and updated): Clinical Practice Guideline for Reducing Pain during Vaccine Injections in Children and Adults

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Introduction

Vaccination is one of humankind's most significant health achievements[1]. Dozens of vaccines developed and implemented worldwide have reduced the burden of infectious diseases and led to significant improvements in global health. Vaccination, however, is not devoid of negative (iatrogenic) effects. The Brighton Collaboration, an international group of scientific experts involved in vaccine safety, identified acute pain at the time of vaccine injection as an adverse event following immunization (AEFI), calling for attention to its assessment and management[2].

Vaccine injection-associated pain impacts individuals receiving the vaccine, health care providers administering the vaccine, onlookers and society at large. Acutely, there is suffering in individuals undergoing vaccination and a negative vaccination experience for them, the health care providers delivering the vaccine and onlookers (e.g., parents, caregivers, siblings)[3-7]. In the long-term, repetitive and/or intensely negative experiences during vaccination can lead to increasingly negative perceptions of vaccination and aversions to or avoidance of future vaccination[3,6-12]. Non-compliance with vaccination compromises individual and societal benefits of immunization by contributing to outbreaks of vaccine-preventable diseases. Individuals who are distressed by needle procedures may engage in broader non-compliant behaviours negatively impacting other aspects of health (e.g., poor glycemic control in individuals with diabetes; poor adherence to weekly injectable medication in multiple sclerosis)[3,7,13,14]. The 2014 World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) Working Group on Vaccine Hesitancy Report identified acute pain at vaccination as a factor underlying vaccine hesitancy and noted mitigation steps as one strategy to consider in addressing this global problem[15].

While caregivers and health care providers may attempt to make vaccine injections comfortable, some interventions that they use are not effective while others that are effective are not used; this contributes to a significant vaccination pain care gap[16-19]. An independent, cross-Canada multi-disciplinary team, the Help ELiminate Pain in KIDS Team (HELPinKIDS), was assembled in 2008 in order to tackle the vaccination pain care gap. The HELPinKIDS team synthesized the research evidence and developed the first ever Clinical Practice Guideline (CPG) on this topic in 2010[20]. The guideline recommendations were incorporated into several national programs and tools, including: an online immunization competency training program developed by the Canadian Paediatric Society, the Rourke Baby Record clinical practice tool[21] and a consumer-directed immunization mobile application or *app* at (http://immunize.ca/en/app.aspx)[22] supported by the Public Health Agency of Canada and the Canadian Public Health Association. In guideline implementation studies, education of immunizers and parents about the recommendations was demonstrated to increase utilization of pain interventions in children undergoing vaccination[23-25].

Two factors informed the decision for an update to the original guideline. Firstly, many new trials have been published for various pain interventions since the original guideline was published, warranting re-examination of original recommendations. Secondly, feedback from team members and external stakeholders revealed that there was interest in adding new domains (clinical questions and expansion of the ages covered) for guidance to attain a more comprehensive approach to the topic.

The purpose and scope for the 2015 guideline was therefore expanded to include: 1) management of acute pain during vaccine injections in the general population across the lifespan, and 2) management of fear in individuals with high levels of needle fear (i.e., individuals with persistent, intense apprehension of or fear in response to a needle procedure; and whereby needles may be endured with intense distress or avoided). The management of the former is distinct from the latter and involves health care providers with vastly different expertise. Hence the guideline was divided into two parts: 1) a general guideline for the management of vaccination-related pain intended primarily for health care providers that administer vaccine injections; and 2) a companion guideline for the management of high levels of needle fear intended primarily for mental health providers. The expanded scope led to a

revision of the team name to 'HELPinKids&Adults.' As with the first guideline, delayed pain (hours to days after injection) was *not* considered as it is distinct from acute (needle) pain[2].

This manuscript summarizes the methodology used in the second version (version 2.0) of the HELPinKids&Adults CPG and the specific recommendations for the part that deals with the management of vaccine-injection related pain. Additional details regarding the methodology and the results of systematic reviews underpinning the recommendations are included in a special issue of the Clinical Journal of Pain which is available open access[26-32]. The systematic review for interventions for high levels of needle fear is included in the supplement issue and the companion guideline is available separately[33,34].

Importantly, pain mitigation during vaccination is considered part of good immunization and clinical practice by the WHO and many of the interventions recommended in this guideline have been promoted for use by the WHO[35].

Process for Development of HELPinKids&Adults 2.0

Review team

Briefly, individuals from the 2008-2010 team were invited to participate in the update. In consultation with stakeholders, additional members were invited to replace and expand representation in the following areas of expertise: pain, fear, pediatrics, family practice, medicine, nursing, pharmacy, psychology, vaccinology, infectious diseases, epidemiology, guideline development, library sciences, public health, family advisory/advocacy, and health policy. All members participated in delineating the scope and purpose of the guideline update, the clinical questions to be included, and reviewed and approved the recommendations. Individuals also participated in different capacities in working groups based on content area and/or methodology expertise and/or interests. Two working groups were convened to specifically oversee the evidence-base (Evidence Lead group) and Knowledge Translation (KT group) aspects of the guideline, respectively. A guideline panel was assembled to review the evidence base and approve the first draft of the recommendations before consideration by the rest of the team and by external reviewers. The Chair and PI (Taddio) oversaw all aspects of the project.

Scope and Purpose

The scope and purpose of the guideline was decided upon using a consensus process at an in-person meeting of the team in February 2014, whereby scoping reviews of the topic and feedback from different stakeholder partners were presented and discussed. It was determined to update and expand the original CPG to include the management of: 1) acute pain during vaccine injections in the general population across the lifespan, and 2) fear in individuals with high levels of needle fear (i.e., persistent, intense apprehension of or fear in response to a needle procedure; these individuals endure needles with intense distress or avoid them). The management of delayed pain (i.e., pain arising at the injection site hours to days after injection) was not included.

The target users for the aspects of the guideline related to acute pain management during vaccine injections are: a) health care providers who administer vaccinations; b) educators, researchers and policy makers (including public health) who develop and evaluate processes of vaccination delivery; c) health care providers who counsel the public about vaccination and pain management; d) industries involved in vaccine development and administration; and e) the public at large.

Health care providers that administer vaccines are not expected to address the management of high levels of needle fear; however, they should be able to identify individuals in need of such treatment. Hence guidance is provided regarding screening for the presence of high levels of needle fear for the purposes of referral to licensed mental health providers with expertise in the treatment of anxiety disorders (e.g., psychologists, psychiatrists) *before* further routine vaccine injections are undertaken. Having a high level of needle fear can interfere with the ability to successfully carry out vaccinations,

reduce the effectiveness of pain treatments, and intensify future fear; thus, only after the high level of needle fear has been adequately treated do we recommend that these individuals undergo routine vaccine injections, with the benefits of pain interventions recommended in the guideline. Vaccination need not be delayed substantially for as little as one session of several hours may be required to successfully treat high levels of needle fear[34].

The target users for the companion guideline[34] about the treatment of high levels of needle fear are licensed mental health professionals with expertise in treating anxiety disorders.

Editorial Independence and Funding

External funding was acquired for the project from the Canadian Institutes of Health Research (CIHR) (KRS 132031). The funding agency did not have any input into the guideline.

All team members signed a conflict of interest form. A process for handling conflicts of interest was developed at the beginning of the project and used to manage financial and intellectual conflicts of interest. Individuals with self-identified conflicts were allowed to participate in all discussions, but were excluded from voting on guideline recommendations in areas of conflict. One government agency representative was an observer and did not participate in voting on recommendations. Individuals from industries either manufacturing or distributing vaccines or pain treatments were excluded from participating.

Guideline Development Methods and Tools

Overview. AGREE-II (Appraisal of Guidelines for Research and Evaluation-II) (www.agreetrust.org) provided the framework for the development of the guideline. The GRADE (Grading of Assessments, Recommendations, Development and Evaluation) (http://www.gradeworkinggroup.org/publications/jce_series.htm) and Cochrane methodologies (http://handbook.cochrane.org/) provided the general framework for the formulation of recommendations and the synthesis of the research evidence.

Choice of Clinical Questions and Outcomes. Clinical questions were identified from the prior guideline, research evidence published in the interim, and clinical practice, and formulated utilizing the PICOS (participants, intervention, comparison, outcome, study design) format (**Box 1**). Forty-seven candidate clinical question stems were initially circulated to the HELPinKids&Adults team and voted upon electronically which covered the management of acute pain during vaccine injections and the management of fear in individuals with high levels of needle fear. Clinical questions for which 2/3 or more of the team voted in favour were included. This process resulted in the selection of 37 preliminary clinical questions. Outcomes for each preliminary question were then selected from a pool of 13 team-identified candidate outcomes (**Box 1**) through a vote. The perspective of the individual undergoing vaccination was prioritized when selecting outcomes (rather than the perspective of other stakeholders – e.g., clinicians, government). Team members independently voted on the importance of each outcome for a given clinical question using a scoring system of 1-9 (higher scores indicating greater importance); voting was carried out electronically. Consistent with the GRADE framework outcomes with a mean score of $\geq$7 were defined as critically important for decision making and consequently prioritized for determination of the recommendations. Outcomes with a mean score of 4-6 were defined as important and included as outcomes of interest to the review; the remainder (mean score <4) were not considered further.

Box 1: PICOS criteria for clinical questions

Item	Definition
P (participants)	Individuals of all ages undergoing vaccine injections in inpatient and outpatient settings, including schools. If no data existed for vaccine injections, then the closest related procedure or context was included (e.g., venipuncture in outpatient clinic).
I (intervention)	Single and combination interventions used for the management of pain* during or related to vaccine injections, including: procedural strategies, physical strategies, pharmacological strategies, psychological (and information provision) strategies, and process (education/implementation) strategies. If no interventions existed for pain during or related to vaccine injections, literature was examined on interventions for the closest related procedure or context (e.g., venipuncture).
C (comparison)	Comparisons included no treatment (i.e., no documented intervention above usual care) or specified comparators (e.g., placebo). Co-interventions were allowed depending on the clinical question. Additive benefits of an intervention over other(s) were also examined separately according to the clinical question.
O (outcomes)	Outcomes included: pain and pain-related outcomes (e.g., fear, distress), preferences, satisfaction, fainting, procedure outcomes (e.g., duration, success), parent fear, knowledge about pain interventions, pain intervention utilization, safety outcomes, vaccine compliance, and/or memory. ***Pain, fear and/or distress were typically prioritized as critically important outcomes across clinical questions.***

At an in-person meeting of the HELPinKids&Adults guideline panel in July 2014, there was a preliminary review and discussion of the research evidence and preliminary recommendations were drafted for the candidate clinical questions. Several clinical questions were removed due to a lack of confidence regarding the applicability of the evidence base to the vaccination context, and others were added to examine particular additive interventions of interest, alterations in the timing or delivery of the interventions, and/or to examine the effects of the interventions separately for individuals of different ages. These changes were electronically reviewed by the panel.

A total of 55 clinical questions were approved for inclusion in the CPG; 49 in the general guideline about the management of acute vaccine injection pain and 6 in the companion guideline about the management of high levels of needle fear. This document includes the recommendations for the 49 clinical questions included in the general guideline. The recommendations for the remaining 6 clinical questions are included in the companion guideline[34].

Delineation of Outcomes. While this guideline focuses on pain as the over-arching patient-important outcome, related constructs such as fear and distress are included (**Box 1**). The constructs of pain, distress and fear are defined in **Box 2**. The evidence is described according to the clinical question and the associated identified critical and important outcomes.

Box 2. Definitions of Pain, Fear and Distress used for the guideline

Pain = Self-rated acute pain (from needle poke and vaccine injection). Delayed pain (hours after injection) was not considered.
Fear = Self-rated negative affect referred to as fear, anxiety, or distress. Fear was separated according to phase of procedure, and could typically include pre-procedural (and post-intervention) and acute (from needle poke and vaccine injection) fear.
Distress (i.e., Pain + Fear) = Observer-rated behaviour referred to as distress, pain, fear, or anxiety, whereby the observer was a researcher, parent or clinician. Distress was separated according to phase of procedure, and could typically include pre-procedural (and post-intervention), acute (0-1 minute after needle poke and vaccine injection) and recovery (1-5 minutes after needle poke and vaccine injection).

The primary assessment method for pain and other subjective outcomes (e.g., fear) was self-report from the person being vaccinated[36]. If self-report was not possible (e.g., young child unable to provide self-report), proxy reports (e.g., caregiver or clinician) and/or observational measures could be used as the primary assessment method[37,38]. Since proxy reports and observational methods typically cannot distinguish between fear and pain, the term used was distress. Self-reported negative affect, fear, anxiety, feeling upset, or distress was termed "fear" for two reasons: 1) it was typically proximal to the procedure and may thus be best conceptualized as fear[39] and 2) to maintain consistency in terminology. As noted above, delayed pain (hours to days after injection) was *not* considered.

Various assessment methods were accepted with face and/or construct validity. Self-reported pain and fear were typically measured with the following global rating scales: Visual Analog Scale (VAS), Numerical Rating Scale (NRS), and faces scales. Behavioural scales (including behavioural indicators of pain such as facial actions, body movements and/or cry) or global rating scales were typically used for observer-reported distress. Physiologic measures reflect overall arousal and were not included as outcomes.

If multiple measures of the same outcome were included in studies (e.g., pain/fear/distress was measured using a Visual Analog Scale (VAS) and faces pain scale), the individual measures were combined into a single score using accepted methods[40]. In addition, outcomes evaluated across various phases of the vaccine injection procedure were analyzed according to the different phases to more precisely describe the effects of the intervention. These phases typically included the pre-procedure (and post-intervention) phase, acute phase (within 1st minute of needle puncture and vaccine injection) and recovery phase (1-5 minutes after vaccine injection) phases. Sometimes phases were combined (e.g., acute and recovery distress).

Search Strategy and Data Extraction and Synthesis. With the assistance of an academic librarian, a broad search strategy was developed to identify relevant articles from the following databases: MEDLINE, EMBASE, PsycINFO, CINAHL and ProQuest Dissertations & Theses Global. The databases were searched from their date of inception; the last update was Feb 26, 2015. No language restrictions were applied. Article citations were reviewed by two individuals and relevant articles were retrieved for full review. Evidence review leads then undertook systematic reviews in their content area. Data were extracted from included studies by at least two reviewers. Data were pooled using accepted methodology and the overall effects were summarized using the Standardized Mean Difference (SMD) for continuous data, or Relative Risk (RR) for dichotomous data, and associated 95% Confidence Intervals (CI). A random effects model was used for all analyses. The detailed search strategy and methodology are described separately in Taddio, McMurtry et al. 2015; *in press*[26].

Quality of Evidence. The risk of bias was assessed for individual outcomes using the Cochrane Risk of Bias tool as interpreted by Hartling et al.[41]. Across studies, the quality was assessed using the GRADE framework, which includes 5 factors: risk of bias, inconsistency, indirectness, precision, and publication bias[42]. The quality of evidence rating across studies for specific outcomes was assigned to four categories: high, moderate, low and very low evidence, all reflecting the degree of confidence in the quantitative measure of benefit or harm suggested by the systematic review[43]. A strict approach was used in the application of GRADE criteria. Evidence profiles and summary of findings tables were created for each clinical question through the GRADE profiler software (version 3.6.1) in which judgments pertaining to the evaluation of the quality of evidence were recorded with an extensive array of explanatory footnotes.

Evidence Interpretation and Summary. Separation of procedure time epochs (e.g., pre-procedure phase, acute phase, recovery phase, and various combinations of phases) were maintained in order to allow for a characterization of the effects of the intervention across the different phases of the procedure. The benefit of an intervention was typically judged according to its effects across all of the procedure phases that were evaluated. In the presence of multiple indicators of a given outcome, some indicators were assigned a higher importance when interpreting overall results; for instance, acute phase distress was valued more highly than distress during other time periods.

If a statistically significant response in favour of the intervention was observed across all indicators of the same critical outcome(s), then an intervention was said to have benefit. If the results were mixed (i.e., evidence of benefit for at least one indicator of the same outcome but not all), then it was said to have some benefit or mixed results. If results were negative for critically important outcomes, the intervention was said to have no evidence of a benefit. Important outcomes were considered in selected circumstances; for example, in the presence of self-reported pain, outcomes of distress could be considered if study participants included young children (e.g., 3-6 years), due to the fact that self-report may not be reliable in this population[36,44,45]. In the absence of data for critical outcomes, important outcomes were considered to estimate treatment effects.

While including different phases of the procedure provided a more detailed characterization of the effects of interventions, it often resulted in downgrading the overall quality of the evidence due to the presence of an insufficient sample size in some analyses (i.e., number of participants was below the recommended optimum information size).

Due to the fact that pain is an iatrogenic harm of vaccination, even small benefits (i.e., Standardized Mean Difference = 0.2) were considered to be clinically significant.

Formulation of Recommendations. Consistent with the GRADE approach, recommendations were issued (rather than neutral or no recommendation positions) for each clinical question, either positive or negative, with an accompanying rationale[46]. The guideline panel considered the following factors in determining the direction and strength of each recommendation: strength of evidence (magnitude of effect, confidence in estimates of effect), balance between benefits and harms, uncertainty about values and preferences, and resource use. Interventions with a larger benefit and higher certainty of benefit were more likely to receive a strong recommendation[47]. The panel prioritized the perspective of the individual being vaccinated over other perspectives (e.g., parents, clinicians, public health, society) and considerations (e.g., economic considerations) when formulating the recommendations.

Recommendations were generally applied to broad developmental stages, including: children 0-3 years, children >3-12 years, adolescents >12-17 years, and adults. There is some overlap in ages across these categories (i.e., children aged 3 and 12 years are included in 2 separate categories) owing to the need to balance (over)-simplification in creating age categories with appropriate guidance, overlap in the underlying literature base, as well as substantial differences in developmental trajectories

of individual children. Where possible and deemed appropriate, further sub-divisions were made, and/or categories collapsed.

Clinical questions included in the guideline are framed in the guideline in reference to a particular comparator unless no treatment/placebo is used. For each clinical question, a brief preamble is provided, followed by a recommendation that includes a description in parentheses of the strength of recommendation (strong, weak) and quality of evidence (high, moderate, low, or very low confidence in estimates of effect). The quality for each recommendation was the lowest quality rating among the outcomes judged as critical. The strength of the recommendation is communicated using the words 'recommend/recommend against' for strong recommendations and 'suggest/suggest against' for weak recommendations. A summary of the evidence base and rationale for the panel's recommendation and implementation (applicability) considerations are then described.

External Review

The AGREE-II methodology[48] provided the framework for external review of the guideline. Firstly, the guideline was reviewed by stakeholder organizations with liaison members on the HELPinKids&Adults team, including: British Columbia Centre for Disease Control, Canadian Center for Vaccinology, Canadian Family Advisory Network, Canadian Paediatric Society, Canadian Psychological Association, College of Family Physicians of Canada, Immunize Canada and the Canadian Public Health Association.

Secondly, we asked external reviewers to review the guideline. External reviewers were comprised of individuals with the relevant content expertise (e.g., pain, guideline methodology), individuals representing stakeholder organizations, or individuals that were members of stakeholder organizations but did not represent them, including: Theresa Agnew (Nurse Practitioners' Association of Ontario), Oliver Baclic (Public Health Agency of Canada), Katie Birnie, Eliana Castillo (Society of Obstetricians and Gynaecologists of Canada), Shelley Deeks (Public Health Ontario), Philippe De Wals (Comité sur l'Immunisation du Québec), Blaine Ditto, Eve Dube (Institut national de santé publique du Quebec), Martine Dubuc (Public Health Agency of Canada), Philip Emberley (Canadian Pharmacists Association), Lucy Gagliese, Frank Gavin (Canadian Child and Youth Health Coalition), Arielle Goldman Smith (Canadian Nursing Coalition for Immunization), Mary Jerrett (Canadian Institute of Child Health), Judith Law (AnxietyBC), Janet McElhaney (Canadian Geriatric Society), Margaret McIntyre (Public Health Ontario), Kathy Reid, Joan Robinson (Canadian Paediatric Society), Anne Smith (Baby Friendly Initiative), Carl von Baeyer, Gary Walco, Kelly Warmington (The Hospital for Sick Children), Arlene Young, and William Zempsky. In addition, the guideline underwent formal review by the WHO Secretariat with an in-person meeting held with representatives of the HELPinKids&Adults team. Individuals involved in this review included: K. O. Antwi-Agyei, Philippe Duclos, Liesbet Goubert, Darunee Jongudomkarn, Kevin Pottie, Nikki Turner, and Winnie Siu. Changes were made to address identified areas of concern. Then the guideline was finalized.

Endorsing and Supporting Organizations:

The guideline is endorsed by the following organizations: Canadian Association of Paediatric Health Centres (CAPHC), Canadian Child and Youth Health Coalition (CCYHC), Canadian Family Advisory Network (CFAN), Canadian Nursing Coalition for Immunization (CNCI), Canadian Paediatric Society (CPS), Canadian Pharmacists Association (CPhA), Canadian Psychological Association (CPA), Canadian Public Health Association (CPHA), College of Family Physicians of Canada (CFPC), Immunize Canada, AnxietyBC, Nurse Practitioners Association of Ontario (NPAO).
The guideline is supported by the following organizations: Canadian Center for Vaccinology (CCfV), British Columbia Centre for Disease Control (BCCDC).

RECOMMENDATIONS FOR THE TREATMENT OF PAIN IN INDIVIDUALS UNDERGOING VACCINE INJECTIONS

Recommendations have been organized into 5 domains (5 P's) of pain management according to the type of intervention: i) Procedural interventions (i.e., injection techniques), ii) Physical interventions (i.e., body position and activity), iii) Pharmacological interventions (i.e., pain medicine), iv) Psychological interventions (i.e., thoughts and behaviours, including information provision), and v) Process interventions (i.e., presence of individuals and educational interventions aimed at implementing various pain management interventions). Additional details are published separately [26-32].

The recommendations are summarized in **Table 1** (**Appendix**) and in 4 treatment algorithms (**Appendix**), whereby recommendations are presented for the different age categories as follows: children up to 3 years, children 3-12 years, adolescents 12-17 years and adults.

i. Procedural Interventions (Injection techniques)

Intramuscular injection technique

Appropriate administration of vaccines is an important aspect of successful immunization (American Academy of Pediatrics, 2012)[49]. Aspiration is a long-standing practice associated with injecting medications intramuscularly, including vaccines. It was adopted as a safety measure in order to prevent accidental intravenous injection[50]. Aspiration involves pulling back on the syringe plunger after the needle is inserted and before the vaccine is injected to check for the presence of blood which would signal that the needle is (inappropriately) in a vein.

The process of aspiration results in a longer tissue needle dwelling time and the potential for lateral movement (wiggling) of the needle in tissue. Together, these factors can increase tissue damage and pain. Because there is little risk of penetrating large blood vessels in the sites routinely used for vaccine injections and the process may add pain, aspiration is no longer recommended[49,51]. Aspiration continues to be performed by many immunizers prior to intramuscular vaccine injections despite recommendations that it is unnecessary[50].

1. Should no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages?

We recommend no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages (strong recommendation, very low confidence in estimates of effect).

Three studies including individuals from infancy to adulthood undergoing vaccination were included in the systematic review[52-54]. There was very low quality evidence for pain and distress (critically important outcomes) due to risk of bias and imprecision. In the single study that included 114 individuals able to provide self-report[54], no evidence of a difference in pain between aspiration and no aspiration groups was demonstrated. Conversely, in two studies including 313 infants, there was a benefit of not aspirating on acute distress:[52,53] [standardized mean difference (SMD) -0.82, 95% confidence interval (CI) -1.18, -0.46)]. The reasons for the differences in results across studies are unclear but may involve other differences in injection technique (e.g., time for aspiration, injection speed, site of injections), as well as painfulness of vaccine used[55]. The results for the studies in infants

were subject to confounding due to the speed of injection (i.e., aspiration and slow injection speed were compared to no aspiration and fast injection).

Implementation Considerations:

Despite the lack of benefit observed for pain from not aspirating from the single study that used self-report[54], the panel strongly recommends against aspiration for individuals of all ages. The rationale for this recommendation includes the lack of need for this step and potential for increased pain due to the longer needle contact time with tissue and potential for increased tissue damage due to sheering action (wiggling) of the needle, particularly if there is movement of the limb and/or needle.

Some immunizers may be concerned by the presence of bleeding at the injection site after vaccination; slight bleeding is common, and does not signal incorrect injection technique[49]. Bleeding at the injection site can be stopped with gentle pressure. No additional resources are required for this intervention. Of note, auto-disable (AD) syringes which preclude the possibility of aspiration are widely used in developing countries for the administration of vaccinations. The costs of such syringes are comparable to traditional syringes (http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.03_eng.pdf?ua=1).

This recommendation differs slightly from the original recommendation in the 2010 HELPinKIDS guideline which promoted *fast* intramuscular injections without aspiration[20]. The original guideline included only one study which combined fast injection and no aspiration[53]. However, there are insufficient data on which to discern the impact of speed on pain. While fast injection may reduce pain due to reduced needle dwelling time and tissue damage, it may also cause pain due to rapid tissue distension. In addition, it is possible that immunizers will miss target injection sites when trying to deliver vaccine injections too quickly. The specific effects of injection speed warrant future investigation.

Order of injection

Some vaccines are inherently more painful than others due to differences in intrinsic properties of the drug, excipients, and/or formulation[56]. At present, it is common and recommended for individuals to receive more than one vaccine injection at a single visit. The order in which vaccines of different 'painfulness' are administered may be important to the overall level of pain experienced by individuals because pain can escalate with each subsequent injection (i.e., increasing sensitivity after repeated painful stimuli, or hyperalgesia)[57] and the vaccine which is administered first determines the starting level of the pain.

2. Should injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages?

We recommend injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages (strong recommendation, moderate confidence in estimates of effect).

Two studies including infants from 0 to 6 months were included in the systematic review[58,59]. There was moderate quality evidence for distress, the critical outcome due to imprecision, and evidence of a substantial benefit when the most painful vaccine was injected last. Included studies compared either: 1) pneumococcus conjugate vaccine, PCV (Prevnar™) to diphtheria and tetanus toxoids, polio, acellular pertussis, and *Haemophilus influenzae* type b conjugate vaccine, DPTaP-Hib (Pentacel™), or 2) Bacille Calmette-Guérin vaccine, BCG (TUBERVAC™) to hepatitis B vaccine (GeneVac-B™). When given first, PCV and hepatitis B caused more pain than DPTaP-Hib and BCG, respectively. Administering the most painful vaccine last (i.e., PCV after DPTaP-Hib and hepatitis B after BCG,

respectively) caused lower overall infant acute distress for both injections (n=196): SMD -0.69 (95% CI -0.98, -0.40).

Implementation Considerations:

This intervention is being recommended due to demonstrated benefit. The results of included studies are being extrapolated to individuals of all ages because the potential for increased pain sensitization following the first injection should it be more painful is present across the lifespan. There are no additional resources required to provide the most painful vaccine last. However, additional research is needed to quantify the amount of pain caused by vaccines that are typically used in combination in clinical practice to inform the order of their administration and to provide clinicians with this information. Vaccine manufacturers should consider and attempt to minimize pain at the time of injection when developing the formulations of vaccines. Examples of painful vaccines include MMR-II™ [60,61], Prevnar™ [58], and Gardisil™ [55].

Simultaneous injections

At present, childhood immunization schedules commonly recommend more than one separate vaccine injection at a single visit. There is the possibility to inject multiple vaccines simultaneously rather than sequentially. On the one hand, rapid administration of both injections at once may help reduce pain due to less sensitization (see recommendation #2) and less anticipatory distress. In contrast, some vaccine recipients (e.g., infants and children) might find it alarming to be approached by more than one clinician from either direction holding a needle at the same time. The potential for differences in how this intervention might work due to differences in these factors led us to examine the effects of this intervention separately for infants and children.

3. Should simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 year?

We suggest simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 year (weak recommendation, low confidence in estimates of effect).

Two studies including infants aged 2 to 6 months undergoing vaccination were included in the systematic review[62,63]. There was low quality evidence for distress (critical outcome) due to risk of bias and imprecision. The results were mixed for different indicators of distress. In the only analysis that included data from both studies (n=172), acute distress was lower in the infants in the simultaneous injection group: SMD -0.56 (95% CI -0.87, -0.25).

Implementation considerations:

The observed benefit of this intervention on some aspects of infant distress led to a weak recommendation for its use in infants. We caution, however, that that some infants may develop ‘stranger anxiety’ over the first year of life, whereby the presence of unknown adults may cause infants to become distressed. The presence of a greater number of adults may therefore exacerbate distress further; in such cases, alternatives to this intervention should be considered. Stranger anxiety is developmentally normal and tends to be present in older infants (greater than 6 months)[64]. Children have been excluded from this recommendation due to lack of certainty of the effects of the intervention and the possibility that it could increase distress (see recommendation #4).

Care is needed to position infants in a comfortable and supportive manner that allows access to limbs for injection, and that neither interferes with other pain management interventions (e.g., breastfeeding, see recommendation #6) or causes undue restraint, which can increase distress further[65].

Additional resources are required to deliver this intervention (i.e., two clinicians to deliver the injections at the same time). In addition, clinicians may be required to alter their own positioning to ensure successful and comfortable administration of injections.

4. Should simultaneous injections be used (rather than sequential injections) during vaccine injections in children >1-10 years?

We suggest <u>against</u> the use of simultaneous injections during vaccine injections in children >1-10 years (weak recommendation, very low confidence in estimates of effect).

One study including children aged 4 to 6 years undergoing vaccination was included in the systematic review[66]. There was very low quality evidence for pain (critical outcome), primarily due to high risk of bias (lack of blinding and standardization of procedures, imbalance in baseline characteristics of study groups) and low sample size (n=44 included in analysis). There was no evidence of a benefit of this intervention on pain: SMD 0.31 (95% CI -0.29, 0.90).

The lack of observed benefit was the primary consideration for recommending against this intervention. The results were extrapolated to the first 10 years of life due to the concern for increased fear (which can increase pain) from the presence of additional immunizers. We also expect there to be substantial alterations in positioning of children and the use of restraint to ensure that simultaneous injections can be administered safely. Delivery of this intervention also requires additional resources (personnel).

We are not confident in the values and preferences of older children (>10 years) and adults with respect to this intervention. It was noted that in a separate study of children aged 11-12 years undergoing vaccinations, children preferred simultaneous injections over sequential injections[67]. Older children (and adults) can be asked about their preferences regarding this intervention.

<u>Site of vaccine injection</u>

Vaccines may be administered in different body regions. At present, the vastus lateralis (a muscle in the anterolateral aspect of the upper thigh) is generally recommended as the primary site for vaccine injections in infants because it provides a large muscle mass; however, the deltoid (a muscle in the upper arm) has also been used. The site chosen may impact the pain and fear experienced due to several factors, including positioning of the individual and physiological differences.

5. Should the vastus lateralis be used (rather than deltoid muscle) during vaccine injections in infants 0-11 months?

We suggest the vastus lateralis be used (rather than the deltoid) as the site of injection during vaccine injections in infants 0-11 months (weak recommendation, low confidence in estimates of effect).

One study including 185 infants aged 4 months undergoing vaccination was included in the systematic review[68]. There was low quality evidence for critical outcomes (distress) due to risk of bias from lack of blinding and imprecision. The results were mixed for the two different indicators of distress included in the study: acute distress and acute and recovery distress combined. For distress during the acute period, the SMD was: 0.11 (95% CI -0.18, 0.40). For distress during the acute and recovery period combined, the SMD was: -0.70 (95% CI -1.0, -0.41).

<u>Implementation considerations</u>:

The suggestion to use the vastus lateralis as the site of vaccine injection in infants 0-11 months is based on observed benefit on aspects of infant distress and lack of additional resources required to

administer this intervention. The use of the vastus lateralis as the site of vaccine injection in infants is consistent with current Canadian recommendations regarding the site of vaccine injection in infants (http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-07-eng.php#rout). It is important to inform parents ahead of time about the anatomical location of vaccine injections for proper use of other pain-relieving interventions such as breastfeeding/holding interventions (see recommendation #6) and topical anesthetics (see recommendation #17).

The impact of this intervention in older children is not known and additional outcomes beyond acute pain (e.g., mobility) may be important to consider. This recommendation is therefore limited to infants in the first year of life. Consideration should be also given to the recommendations for injection sites and needle sizes made by expert organizations involved in immunization policy.

ii. Physical interventions (body position and activity)

Breastfeeding

Breastfeeding is one of the most significant factors in promoting optimal health and development in children and is the normative standard for infant feeding and nutrition[69]. The WHO recommends breastfeeding for up to 2 years or beyond (http://www.who.int/nutrition/topics/infantfeeding_recommendation/en/). Within the context of vaccination, there is evidence that breastfeeding may improve the effectiveness of some vaccines and reduce fever associated with vaccine injections[70,71].

For this guideline, breastfeeding was specifically evaluated for its effectiveness in reducing distress in young children during 2 different time points relative to vaccine injections: 1) during needle puncture and administration of the vaccine (recommendation #6) and 2) beforehand (i.e., before needle puncture and administration of the vaccine; recommendation #7). When used during vaccine injections, breastfeeding is hypothesized to reduce distress via multiple mechanisms, including: physical comfort, sucking, distraction and ingestion of sweet-tasting and other substances that may have, individually and together, pain and distress-relieving effects. When used before vaccine injections, breastfeeding may reduce distress via satiation of infants, which may promote calmness during needle procedures.

Previous systematic reviews have demonstrated the effectiveness of breastfeeding undertaken during needle procedures in neonates and infants[72,73] and breastfeeding is used in hospital settings to reduce needle-related pain[74].

6. Should breastfeeding be used during vaccine injections in children 0-2 years?
We recommend breastfeeding be used during vaccine injections in children 0-2 years (strong recommendation, very low confidence in estimates of effect).

Nine citations including data from 8 separate studies that examined breastfeeding **during** vaccination were included in the systematic review[75-83]. There were 4 different measures of distress (critical outcome) with quality ranging from low to very low. Data from 8 citations (7 separate studies) including 792 infants reported data for acute distress[75,77-83] . The quality of evidence for this indicator of distress was low, downgraded for risk of bias due to lack of blinding and lack of consistent randomization across included studies. The SMD was -1.78 (95% CI -2.35, -1.22). The other distress outcomes included between one and four studies and all demonstrated a benefit of breastfeeding.

Implementation considerations:

The strong recommendation in favour of breastfeeding is due to the substantial benefit of breastfeeding on pain mitigation. While studies have not evaluated the effects of breastfeeding beyond 12 months, some infants may be breastfed beyond 12 months, thus potentially benefiting from the intervention. The panel recommended its use up to 24 months because we place a high value on

breastfeeding and breastfeeding is feasible (fast onset of action, cost-neutral, easy-to-administer). This recommendation is also consistent with the WHO's recommendation to continue breastfeeding for up to 2 years or beyond (http://www.who.int/nutrition/topics/infantfeeding_recommendation/en/).

Breastfeeding should be commenced before needle puncture and vaccine injection(s) and continued during and after injection(s). It may take a few minutes for an adequate latch to be established. The mother can be asked to confirm that the infant is properly latched prior to vaccination. A latch may be recognizable by the presence of a large amount of areola in the mouth, flanged lips and active jaw movement[84]. Limbs can be exposed during breastfeeding to allow vaccine injections to be administered.

Some infants may temporarily interrupt breastfeeding during vaccination because of crying. There are no reports of adverse effects, including: aspiration, cyanosis, respiratory changes, or vomiting. When breastfeeding is interrupted because of infant crying, mothers can pause and then gently encourage infants to resume breastfeeding. The infrequency of vaccine injections relative to breastfeeding makes it unlikely that infants will learn to associate breastfeeding with pain.

There are no additional resources identified that are required to provide breastfeeding to infants. Mothers are usually present during vaccine injections, making breastfeeding a feasible intervention. A private area is recommended. The inconvenience to health care providers to alter their office activities to ensure that mothers have time to establish an adequate latch is considered minor and office activities can be planned to account for this time. This time may be also offset by less time taken after the appointment to soothe distressed infants. Health care providers may consider using a seated position during vaccine injections in order to facilitate successful and comfortable injections.

Alternatives to breastfeeding should be considered in the event that breastfed infants and/or mothers choose not to breastfeed or infants are normally fed by other methods. For example, a baby can be held and bottle-fed with expressed breast milk or formula throughout the procedure. This simulates aspects of breastfeeding and may confer benefit, including: physical comfort, sucking, and ingestion of sweet-tasting substances (see also recommendations #8, #9, #12, #22, #23, #24).

7. If breastfeeding is not used during vaccine injections (see recommendation #6), should breastfeeding be used before vaccine injections in children 0-2 years?

If breastfeeding is not used during vaccine injections, we suggest breastfeeding before vaccine injections in children 0-2 years (weak recommendation, low confidence in estimates of effect).

Two trials including 100 infants aged 6 weeks to 3 months investigated the effect of breastfeeding *before* vaccine injections[85,86]. The timing when breastfeeding ended was 2 minutes to 1 hour before vaccination. There was moderate to low quality evidence across all distress outcomes (critical outcome) due to risk of bias and imprecision. In the only analysis that included data from both studies, acute distress was lower in the infants in the breastfeeding group: SMD -1.43 (95% CI -2.14, -0.72). The results were mixed for other distress outcomes; a benefit was demonstrated for acute and recovery procedure distress, but not for recovery distress.

Implementation considerations:

This intervention is being suggested due to demonstrated benefit in aspects of infant distress. This age limit is extended to the first 2 years of life to coincide with recommendation #6 (i.e., potential for benefit across this age range, practicality, and consistency with current global recommendations for the duration of breastfeeding (http://www.who.int/nutrition/topics/infantfeeding_recommendation/en/).

While there are no additional resources required to provide breastfeeding to infants, some planning is required for this intervention. If the intervention is being applied in the vaccination clinic, a private area is recommended for mothers and babies to facilitate this intervention. Health care providers may have to alter office practices and plan activities to accommodate this intervention. The inconvenience is

considered minor and may be offset by less time taken after the appointment to soothe distressed infants. It is important to note that the use of this intervention does not preclude the use of other interventions (e.g., see recommendations #6, #9, #17).

Positioning

Individuals may be positioned in various ways during vaccine injections (e.g., sitting, lying supine), which may influence how they feel and experience vaccination. Methods of positioning that are comfortable and promote a sense of control for the individual undergoing vaccination have been promoted[65]. Lying supine is not generally recommended because it may be uncomfortable and induce fear due to a perceived lack of control[87].

Some of the interventions included in this guideline imply particular positioning methods (e.g., breastfeeding implies holding); however, most do not. A specific positioning intervention recommended for neonates is skin-to-skin contact/care (also known as 'kangaroo care'), which involves placing a diaper-clad baby prone on the mother's bare chest. Skin-to-skin contact has been evaluated for its effectiveness in reducing distress during medical procedures in neonates and demonstrated to have some benefit[88]. For infants and young children, they can be held on a parent's lap in a gentle hug. Older children and adults can sit on their own in an upright position.

8. Should skin-to-skin contact be used during vaccine injections in neonates 0-1 month?
We recommend skin-to-skin contact during vaccine injections in neonates 0-1 month (strong recommendation, moderate confidence in estimates of effect).

Three studies including 736 neonates in the first three days of life undergoing vaccination were included in the systematic review[89-91]. Skin-to-skin contact was initiated at least two minutes before vaccine injection(s). There was moderate quality evidence for distress (critical outcome) primarily due to risk of bias from lack of blinding. There was evidence of benefit of this intervention for both indicators of distress included in the studies (i.e., procedural acute distress, procedural recovery distress). For the acute phase of the procedure, the SMD was -0.65 (95% CI -1.05, -0.25). For the recovery phase of the procedure, the SMD was -0.89 (95% CI -1.26, -0.52).

Implementation considerations:

This intervention is being recommended due to demonstrated benefit. While the results are limited to neonates in the first days of life, the recommendation has been applied to neonates across the first month of life as other studies of this intervention have included this age range[88]. However, this recommendation only applies to infants who are not breastfed during vaccine injections. If an infant is breastfeeding, then breastfeeding is preferred to reduce distress during vaccine injections (see recommendation #6).

There are no additional resources required to provide this intervention. A private area is recommended and a blanket to cover the baby and caregiver. The usual setting for this intervention is the hospital, after the birth of an infant. The effectiveness of this intervention when applied by individuals other than the mother (e.g., father) is not known. In limited data in hospitalized neonates, there was no evidence of a difference when this intervention was delivered by a different individual, including the father or an alternate female[88]. Clinicians may choose to administer vaccine injections in a seated position to facilitate successful and comfortable administration.

9. Should holding be used (rather than lying supine) during vaccine injections in children 0-3 years?
We recommend holding be used (rather than lying supine) during vaccine injections in children 0-3 years (strong recommendation, very low confidence in estimates of effect).

Three studies including 213 infants aged 6 weeks to 6 months were included in the systematic review[92-94]. The intervention consisted of holding of the infant by a parent. Holding was initiated before vaccine injection(s) and continued during and after injection(s). There was low to very low quality of evidence across the different indicators of infant distress (critical outcome) due to risk of bias, inconsistency and imprecision. There was no evidence of a benefit of holding. In the only analysis that included all studies (n=213), the SMD for acute infant distress was -0.72 (95% CI -1.95, 0.51). However, there was contamination of the control (lying supine) group in one of the studies (i.e., some infants in the supine group were picked up and held immediately afterwards) (Ipp, et al., 2004)[93]. Removal of the data from this study led to an upgrading of quality of evidence to low and a benefit in acute distress (n=107): SMD -1.25 (95% CI -2.05, -0.46). The results were not significant for the analysis on the other distress outcome (i.e., acute and recovery procedural distress); however, the data were obtained from the same study (i.e. Ipp, Taddio et al., 2004)[93].

Implementation considerations:

Holding is strongly recommended over lying supine due to the observed benefit on acute distress (without the data from Ipp, Taddio et al., 2004)[93]. In addition, close proximity soothing is regarded as a developmental need for infants in distress[95]. This recommendation applies to children in the first 3 years of life who are not breastfed or receiving skin-to-skin contact (neonates) during vaccine injections. While the evidence only includes young infants in the first year of life, older children are expected to benefit from holding.

This intervention is feasible and does not require additional resources. Infants can be held in a gentle hug on the parent's lap with limbs exposed (e.g., legs can be positioned on either side of parent's torso so that they are accessible to the clinician administering the vaccine(s)). Parents can gently place their arms over the child's arms. Forcible restraint (e.g., child being held down) should not be used as it can increase fear and distress[65]. Sitting is recommended for the adult holding the child to prevent falls. Clinicians may also choose to sit to facilitate successful and comfortable administration of injections.

10. If holding is not used during vaccine injections (see recommendation #9), should a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 years?
We recommend a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 years who are not held during vaccine injections (strong recommendation, low confidence in estimates of effect).

Two studies including infants aged 1 day to 4 months were included in the systematic review[96,97]. In both studies, infants were lying supine during vaccine injections and the intervention included a combination of interventions delivered after vaccine injections (e.g., holding, patting and/or rocking) by clinicians. The way parents usually comfort their infants after vaccination was the comparison condition. There was low quality evidence for distress (critical outcome) due to risk of bias and imprecision. There was evidence of a benefit of this intervention across the different indicators of distress that were assessed: distress during the acute phase and distress during acute and recovery phase. In the analysis including the data from both studies (n=417), there was a benefit of the intervention for distress during the acute and recovery phase: SMD -0.65 (95% CI -1.08, -0.22).

Implementation considerations:

This recommendation applies to children in the first 3 years of life who are not breastfed, held or given skin-to-skin contact during vaccine injections. While the evidence only includes infants up to 4 months, this recommendation is extended to older infants and children as the panel values optimizing physical comfort; soothing of children during vaccine injections is also regarded as a developmental need[95].

This intervention typically involves adults in a standing position; however, it can be delivered while seated. In included studies, the intervention was administered by a trained clinician and parents would therefore require some education to deliver this intervention. The amount of training is considered minor. As stranger anxiety tends to be present in older infants (greater than 6 months)[64], it may impact the success of this intervention in older infants if provided by a clinician.

11. Should sitting upright be used (rather than lying supine) during vaccine injections in children >3 years and adults?

We recommend sitting upright be used (rather than lying supine) during vaccine injections in children >3 years and adults (strong recommendation, low confidence in estimates of effect).

One study including children aged 4 to 6 years undergoing vaccination was included in the systematic review[87]. There was low quality evidence for critical outcomes (fear, pain) due to risk of bias and imprecision. The results were mixed: a benefit was observed for fear [n=107: SMD -0.39 (95% CI -0.77, -0.01)] but not for pain [n=107: SMD: 0.07 (95% CI -0.31, 0.45)]. We considered the results for distress given that the children were of an age where self-report may not be reliable[44,45]. Both measured distress indicators (i.e., pre-procedure distress and acute and recovery distress combined) demonstrated a benefit of the intervention. For acute and recovery distress combined, the SMD was -10.3 (95% CI -20.18, -0.42). There were no identified undesirable consequences.

Implementation considerations:

Sitting upright is strongly recommended for individuals who can sit up on their own or with assistance. Sitting up is believed to reduce fear because it promotes a sense of control. Children can be positioned on a parent's lap and supported in a comfortable way (e.g., side-sitting or chest-to-chest in a hug with legs on either side of parent's lap), which can also assist with keeping the limb to be vaccinated still. Limbs can be exposed as described in recommendation #9 above. Avoid forcibly restraining children as this can increase fear[65]. Children, adolescents and adults can sit on their own. There are typically no additional resources required to provide this intervention (chairs may be made available) and this intervention is feasible to implement. Clinicians may choose to sit to facilitate successful and comfortable administration of injections.

Caution is recommended in individuals with a history of fainting; providing support or reclining may avoid falls from a seated position. Alternatively, muscle tension may also be used (see recommendation #16). Individual preferences should be considered.

Non-nutritive sucking

Non-nutritive sucking is defined as sucking not relating to or providing nutrition and is recognized for its pacifying effects in infants[98]. Non-nutritive sucking can be achieved using a variety of methods, including finger/thumb or an external device (pacifier/soother). Non-nutritive sucking has been the subject of much research and controversy regarding its potential effects, both negative and positive (reviewed in Nelson, 2012[99]). For the purposes of this guideline, a summary of the research evidence regarding its effectiveness specifically for reducing distress during vaccine injections was reviewed. The mechanism of action of non-nutritive sucking in this context has been hypothesized to involve the

activation of orotactile and mechanoreceptors, which may inhibit nociception or provide distraction[100]. There is evidence for the efficacy of non-nutritive sucking in neonates undergoing procedures[101].

12. Should non-nutritive sucking (using a thumb/finger, pacifier) be used during vaccine injections in children 0-2 years?

We suggest non-nutritive sucking (using a thumb/finger pacifier) be used during vaccine injections in children 0-2 years (weak recommendation, low confidence in estimates of effect).

Two studies including infants 0-4 months of age undergoing vaccination were included in the systematic review[102,103]. There was low quality of evidence across the different outcomes of distress (critical outcome) due to risk of bias and imprecision and evidence of a benefit of the intervention across the different indicators of distress evaluated: acute, acute and recovery, and recovery. In the only analysis containing data from both studies (n=186), the SMD was -1.88 (95% CI -2.57, -1.18) for acute distress. The rate of sucking may be an important factor for success of this intervention; included studies, however, did not determine sucking rate.

Implementation considerations:

This intervention is suggested for children in the first 2 years of life who are not being breastfed during vaccinations and engage in either thumb/finger-sucking or sucking on pacifiers. This recommendation is restricted to the management of procedural distress and does not address the use of non-nutritive sucking outside of the context of vaccine injections. Children that regularly use pacifiers can be offered their own pacifier; hence, there are no additional resources required for this intervention. An adult may be required to assist by gently holding the device or finger/thumb in place to stimulate sucking and to prevent it from falling out of the child's mouth.

The ability of children to engage in self-soothing behaviours during times of distress is valued. Some children offered this intervention may refuse to suck and other interventions should be offered. This intervention does not preclude the use of other interventions (e.g., see recommendations #8, #9, #17, #22, #23).

Tactile stimulation (manual and vibratory)

Stimulation of the skin (tactile stimulation) either adjacent to the site of a simultaneously occurring painful medical procedure or on the contralateral side has been evaluated for its analgesic effects during various needle procedures. Tactile stimulation is typically delivered either manually, by rubbing, stroking or applying pressure, or with the application of a vibrating device. The proposed mechanism of action of this intervention involves the gate control theory and the notion that the touch sensation competes with the pain sensation to reduce the pain signal to the brain[104,105].

13. Should manual tactile stimulation be used during vaccine injections in individuals of all ages?

We suggest against manual tactile stimulation during vaccine injections in individuals of all ages (weak recommendation, very low confidence in estimates of effect).

Six studies including individuals ranging in age from infancy to adulthood undergoing vaccination were included in the systematic review[106-111]. There was moderate to very low quality evidence for critical outcomes (pain and distress), in part due to high risk of bias, inconsistency and imprecision. There was no evidence of a benefit for pain in the three studies including participants capable of self-report (n=893): SMD -0.38 (95% CI -0.96, 0.21). Similarly, there was no evidence of a benefit for any indicator of distress in three studies including participants unable to provide self-report. In the analysis of acute distress that included all three of the relevant studies (n=301 participants), the SMD was -0.69

(95% CI -1.77, 0.39). The evidence base included heterogeneity in the delivery of the intervention, type of injection, and co-interventions.

This recommendation differs from the original recommendation in the 2010 guideline which promoted tactile stimulation in children 4 years and older[20]. The original guideline included only one study in children[110]. Aspects of the intervention and the process of administering vaccines (e.g., pinching the skin or securing the limb) used in additional trials may have introduced contamination that offset the benefit of this intervention. Based on the cumulative available data, which does not demonstrate an overall benefit of this intervention, it is no longer being recommended for general use. Consistent with these data, there are other negative studies that used an external pressure device (i.e., ShotBlocker) to deliver the tactile stimulation rather than manual tactile stimulation[112,113].

14. Should tactile stimulation using an external vibrating device and cold be used during vaccine injections in children >3-17 years?

We suggest a vibrating device with cold be used during vaccine injections in children >3-17 years (weak recommendation, low confidence in estimates of effect).

Two studies including children from 4 to 7 years were included[114,115]. In one study[115], a vibrating device decorated as a bee with an ice pack attached to the underside (Buzzy™) was applied by a researcher on the arm being vaccinated just above the injection site and kept there until the end of the injection. In the other study[114], a multi-faceted tactile intervention was used, including: a vibrating device applied to the contralateral arm in the form of a game, and an external tactile device pressed on the skin on the ipsilateral side. In addition, a vapocoolant (see recommendations #26-28) was sprayed on the vaccination site immediately before injection. The quality of evidence for the critical outcomes (pain, fear) was low due to risk of bias (lack of blinding) and imprecision. There was a benefit on pain (n=145): SMD -1.23 (95% CI -1.58, -0.87). There was no evidence of a benefit for fear (n=104): SMD 0.28 (95% CI -0.11, 0.66). The contributions of cold and distraction to the effectiveness of both of these tactile interventions are not known.

Implementation considerations:

Based on the demonstrated benefit of this intervention, it is suggested for reducing vaccine injection pain. While the evidence base only included children up to 7 years, the recommendation has been extended to older children because of supporting evidence of the effectiveness of this intervention in children up to 18 years in a related context (i.e., venipuncture)[116,117].

This intervention requires additional resources for implementation, including: cost of supplies (i.e., vibrating devices), and personnel/time to administer them. One recent study trained parents to administer the multi-faceted tactile stimulation intervention in order to avoid the need for additional personnel[118].

Individual preferences should be considered when implementing this intervention. Consideration should be given to the cold sensation produced from the Buzzy™ or vapocoolant spray as it may lead to discomfort in some individuals (see recommendations #26-28). It is possible to deliver the tactile component of both interventions without the cold component although the effectiveness of doing so is not known. While this recommendation is limited to children, there is the potential for adults to benefit; however, future research is recommended, including determination of the preferences of adults for this intervention.

Warming the vaccine

Injectable medications that deviate from normal body temperature in either direction (i.e., higher or lower) may activate nociceptors, leading to the sensation of pain. Altering the temperature of medications has therefore been undertaken to try to counter the potential pain-inducing effects. With respect to vaccines, they are usually refrigerated and their cold temperature may contribute to the pain experienced by individuals during administration.

15. Should warming the vaccine be used before vaccine injections in individuals of all ages?
We suggest against warming the vaccine before vaccine injections in individuals of all ages (weak recommendation, low confidence in estimates of effect).

One study including 150 adults was included in the systematic review whereby vaccines were warmed (either by rubbing or by an incubator) immediately prior to injection or not[119]. There was low level quality of evidence for the outcome of pain (critically important outcome) due to risk of bias and imprecision and no evidence of a benefit of warming the vaccine: the SMD was 0.02 (95% CI -0.32, 0.36). Of note, the vaccine temperature in no warming group approximated room temperature and the vaccine temperature in the intervention group was higher by approximately 10 degrees centigrade.

This intervention is not recommended due to the lack of observed benefit. This recommendation is being extrapolated to all ages as there is no reason to believe that the results would differ across the lifespan. Temperatures that are closer to body temperature may be required to have an observable impact on pain, as suggested by a previous systematic review of warming local anesthetics prior to injection which showed that warming to body temperature effectively reduced infiltration pain[120]. Alternatively, the temperature observed in the control group may have been sufficiently high compared to usual refrigerated temperatures that it approximated an active treatment and was not sufficiently cooler than the warmed vaccine for warming to have demonstrated a benefit. It is also important to consider the effect of warming vaccines on their biologic activity. Correct storage and handling of vaccines is of paramount importance to their effectiveness.

Muscle tension (for individuals with a history of fainting)

Fainting (syncope) can occur during vaccine injections and represents a significant safety concern[121-124]. In fact, pain and seeing blood/needle procedures are included in the top five triggers for fainting[125]. Fainting is typically attributed to a vasovagal response. The pathophysiology involves an initial (typically normative) increase in heart rate and blood pressure followed by (over)compensation by the body resulting in a rapid drop in heart rate and blood pressure. The drop in blood pressure results in reduced cerebral blood flow, which can then lead to a loss of consciousness (fainting). Fainting can occur in individuals with and without needle fear but the vasovagal response appears more common in individuals with an extreme fear of blood and needles (70% and 56% respectively)[126]; see the companion guideline for use of muscle tension in individuals with a high degree of needle fear[34]. The peak age of onset of vasovagal syncope appears to be in mid-adolescence for both males and females; the lifetime prevalence has been estimated at 35% in the adult (35-60 years) general population[125]. Fainting can result in serious injuries due to falling[121-124].

Muscle tension is designed to increase blood pressure and cerebral blood flow in order to combat the vasovagal response and subsequent fainting in individuals with a history of fainting. In this intervention, an individual learns to tense muscles of the body and can also learn the signs of a drop in blood pressure (i.e., prodromal vasovagal signs) so that the tension technique can be utilized to prevent the onset of symptoms and/or arrest them once they appear. Muscle tension is achieved using two different approaches. The cyclical variant involves tensing a given set(s) of muscles (arms, legs, and/or torso) until a feeling of warmth is experienced in the face (10-30 seconds) and then releasing the

tension (20-30 seconds) and repeating this sequence until the perceived threat of fainting is diminished. It is important to note that releasing the tension is not the same as relaxing; rather, it involves returning to baseline only. The second approach involves holding the tension as long as possible or until symptoms diminish[127,128]. In both approaches, the individual breathes as he/she normally would.

16. Should muscle tension be used for vaccine injections in children ≥7 years and adults with a history of fainting?

We suggest muscle tension be used for vaccine injections in children ≥7 years and adults with a history of fainting (weak recommendation, very low confidence in estimates of effect).

Three studies including 286 individuals in mid to late adolescence through older adulthood were included in the systematic review; however, none were undergoing vaccine injections[127,129,130]. The variants of muscle tension used in the included studies were leg tensing, leg crossing (e.g., crossing legs, tensing leg, buttock, and abdominal muscles), arm tensing (e.g., tensing both arms by one hand gripping the other and trying to pull them apart/abducting), and/or handgrip (e.g., tightly gripping a ball or other object in dominant hand). Both cyclical -1 study[130] and holding -2 studies[127,129] methods were used. Methods of training were variable and included demonstration, instruction, practice with biofeedback, photos of maneuvers, as well as supervision and feedback. There was very low quality of evidence for critical outcome (fainting) due to risk of bias (lack of blinding), indirectness (individuals were not undergoing vaccine injection) and imprecision. The results were mixed for different indicators of fainting. Tension resulted in benefits with respect to fainting both acutely during a procedure [n=38: RR 0.11 (95% CI 0.02, 0.79)] number of patients who fainted during a 12-month follow up [n=208: RR 0.62 (95% CI 0.44, 0.88)] and number of fainting episodes per patient per year [n=208: SMD -3.32 (95% CI -3.74, -2.90)]. The intervention did not alter post-procedural fainting (although the tension had ceased at that time), or time to recurrence of fainting at follow up.

Implementation considerations:

We recommend use of screening questions for assessing history of fainting reactions in order to determine if an individual should be considered for this intervention. Additional information about fainting and a description of screening questions that can be used to identify individuals with fainting is included in the section titled "**Additional Tools for Guideline Implementation**" following the recommendations.

Additional resources are required to train individuals to use this technique. These resources are considered justified to mitigate potential injury that can occur if an individual faints during or after vaccination[121-124]. Methods of instruction include one on one instruction and videos. One on one instruction in muscle tension can occur 5-10 minutes prior to vaccination and include verbal instruction and modeling of the technique with several minutes of practice. While arm tension alone has been used, we recommend including the lower body (i.e., leg and abdominal tensing) in order to maximize changes in blood pressure. If arm tension is used, it should be used in conjunction with lower body tension and focused on the non-vaccinated arm as increasing tension in the vaccinated arm may make it harder to inject; a ball or other object may be helpful but does not appear to be required. Using imagery (e.g., asking the individual to imagine squeezing a lemon, holding a pencil between his/her knees, flexing abdominal muscles as if someone is about to step on his/her stomach) may be helpful in administering the technique. A 2-minute video exists for the blood donation context[131-133] where muscle tension has been recommended as a strategy to prevent fainting[134]. Muscle tension should begin prior to vaccination and continue for several minutes afterwards or until the individual is not experiencing prodromal vasovagal signs (e.g., nausea, dizziness, sweatiness, visual disturbances).

This intervention is considered practical for implementation in school-based vaccination programs. Although younger children have been reported to have demonstrated vasovagal syncope[135], the success

of this intervention is unknown in that population. The age of 7 years was selected as a cut-off for several reasons: 1) the peak onset of fainting occurs in later childhood, 2) children of this age possess the cognitive abilities to learn this technique and to comply with this intervention, and 3) clinicians administering vaccine injections in different settings would be reasonably expected to be able to train children of this age in the use of this intervention on the day of vaccination.

Caution is recommended with respect to positioning during vaccine injections to avoid falls; supported or a reclined sitting position are possible options (see recommendation #11). Alternately, lying down is possible. Individual preferences should be considered. Patients may prefer to lie down to avoid fainting. Slow transitions between positions (e.g., supine to sitting up to standing) and avoidance of prolonged standing may help reduce risk of fainting responses[134].

iii. Pharmacological interventions (Pain medicine)

Topical Anesthetics

Topical anesthetics are local anesthetic-containing creams, gels and patches that are applied to the skin and penetrate through the superficial layers to block transmission of nociception via sodium channel blockade[136]. They are commonly used to treat pain from a variety of superficial skin procedures, including needle insertion, and have been demonstrated to be safe and effective in individuals of all ages, including young infants[137-139].

The panel evaluated the effectiveness of topical anesthetics when used during vaccine injections across the lifespan, but separated the analysis by age (≤12 years and >12 years) to account for potential differences in preferences regarding this intervention (recommendations #17 and #18). Separately, the additive effect of breastfeeding when combined with topical anesthetics was examined in young children (recommendation #19).

17. Should topical anesthetics be applied before vaccine injections in children 0-12 years?

We recommend topical anesthetics be applied before vaccine injections in children 0-12 years (strong recommendation, very low confidence in estimates of effect).

Fifteen studies including children in the first 12 years of life undergoing vaccine injections were included. The majority of studies investigated pain during intramuscularly injected vaccines; the remainder investigated either subcutaneously injected vaccines or combinations of intramuscular and subcutaneously administered vaccines[75,85,140-152]. The topical anesthetic preparations evaluated included: lidocaine-prilocaine 5% cream or patch (EMLA™) and amethocaine 4% gel (Ametop™). The majority of included studies were carried out in young children unable to provide self-report of pain; hence, the critical outcome was distress. The quality of evidence for this outcome ranged from moderate to very low due to risk of bias with or without imprecision. The results were mixed for different indicators of distress; most analyses, however, included data from only 1 or 2 studies. In the analysis with the largest number of included studies (n=13 with 1424 children), there was a substantial benefit of topical anesthetics on acute distress: SMD -0.91 (95% CI -1.36, -0.47).

Three studies including children aged 4 to 11 years included self-reported pain[142,143,152]. The quality of the evidence was moderate to very low, due to risk of bias and imprecision. The results of the meta-analysis including all studies showed no evidence of benefit: SMD -0.29 (95% CI -0.64, 0.05). Excluding data from one study with a high risk of bias due to lack of blinding, co-intervention and vaccination of children in groups (Cohen et al., 1999)[143], there was low quality evidence for this outcome and evidence of benefit: SMD -0.47 (95% CI -0.73, -0.21). The same study by Cohen et al. (1999)[143] included data for fear (critical outcome) and found no evidence of a benefit for this outcome.

Implementation considerations:

The panel strongly recommends the use of topical anesthetics for children in the first 12 years of life to reduce pain during vaccine injections due to demonstrated benefits on indicators of distress and pain. Topical anesthetics are a well-established therapy for the mitigation of needle-related pain across the lifespan[137-139]. For young children in particular, who cannot advocate for themselves and are at risk of long-term harm from unmitigated pain due to the development of needle fears and future noncompliance behaviours, the provision of topical anesthetics should be a standard preventative measure. The values and preferences of children for pain care were considered in the formulation of this recommendation. The majority of children are afraid of needles, and report a preference for analgesics to be used [6,153].

Clinicians administering vaccinations, parents of children undergoing vaccination, and children undergoing vaccination should be instructed on the application of topical anesthetics, including location, dose and timing. In Canada, three commercial preparations are available for sale in pharmacies without a prescription: lidocaine-prilocaine 5% cream or patch, tetracaine 4% gel, and liposomal lidocaine 4% cream. Because currently available topical anesthetics require between 20 and 60 minutes (depending on the brand) for adequate anesthesia, it is necessary to plan for their use. They can be applied prior to arrival at the vaccination setting or upon arrival, depending on the usual waiting times and parent and/or individual preferences.

The usual dose is 1 g, which is equivalent to a mound of gel or cream the size of a nickel. If vaccine injections are planned for two separate anatomical sites (e.g., left and right arm), apply to both sites. Topical anesthetic creams and gels are typically covered by an occlusive dressing (usually Tegaderm™) to enhance skin penetration and prevent them from being accidentally wiped off the skin.

It is important to note that topical anesthetics may not remove all sensation from vaccine injections; individuals can be informed that they may feel some pressure from the injection (which is typically not painful). Common side effects include temporary skin color discoloration, including erythema and blanching. Discomfort from removal of the occlusive dressing can also occur. To minimize this from happening, stretch the dressing horizontally away from the skin rather than upwards and it will separate from the skin. Alternatively, cover the preparation with plastic wrap (e.g., Glad Press 'N Seal™) which can be wrapped on and/or around the limb. Systemic toxicity and allergic reactions are rare[136,154]. While currently available topical anesthetics such as lidocaine-prilocaine are not currently recommended for use by the product monograph in infants < 3 months, there are data demonstrating safety in this population[139] and they are used in this population in hospital settings[155].

There is no evidence of a negative effect of topical anesthetics on immune response to vaccines. In three studies included in the systematic review, there was no demonstrated effect on antibody responses to measles-mumps-rubella (MMR), diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenza* type b conjugate (DTaP-IPV-Hib) and hepatitis B. Separately, a controlled trial by Dohlwitz et al (1998)[156] reported no effect of topical anesthetics on immune response to Bacillus-Calmette-Guérin (BCG) vaccine. These results are being extrapolated to other vaccines.

Extra resources are required for this intervention (i.e., cost of intervention and cost of education). Some individuals and caregivers may agree to pay for topical anesthetics. Alternatively, they can be provided by settings administering vaccinations.

18. Should topical anesthetics be applied before vaccine injections in adolescents >12 years and adults?

We suggest topical anesthetics be applied before vaccine injections in adolescents >12 years and adults (weak recommendation, moderate confidence in estimates of effect).

Two studies including adolescents and adults that evaluated topical anesthetics (lidocaine-prilocaine 5% cream) for vaccine injection pain mitigation were included in the systematic review[157,158]. There

was moderate quality evidence for the critical outcome of pain. In the single study included in the meta-analysis for critical outcomes[158] with 60 participants, there was a benefit of the intervention on pain: SMD -0.85 (95% CI -1.38, -0.32).

Implementation considerations:

The panel weakly recommended the use of topical anesthetics in adolescents and adults to reduce pain during vaccine injections as individual preferences for this intervention are expected to be highly variable in this population, according to level of concern about pain. Individuals can be asked about their preferences. For additional information regarding this intervention, see recommendation #17.

19. 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 years?

We suggest combining topical anesthetics before vaccine injections and breastfeeding during vaccine injections in children 0-2 years (weak recommendation, low confidence in estimates of effect).

One study involving 60 infants aged less than 3 months undergoing vaccination was included in the systematic review that compared topical anesthetics (i.e., lidocaine-prilocaine 5% cream) alone to topical anesthetics and breastfeeding together[145]. There was low quality of evidence for distress (critical outcome) due to risk of bias and imprecision. The results were mixed for different indicators of distress: positive for distress during acute and recovery phase combined [SMD -0.83 (95% CI -1.36, -0.30)] and recovery phase alone [SMD -1.01 (95% CI -1.55, -0.47)], and negative for acute distress [SMD -0.35 (95% CI -0.86, 0.16)].

Implementation considerations:

The combination of topical anesthetics and breastfeeding is suggested because of a demonstrated benefit above the use of topical anesthetics alone (i.e., additive effect) for some indices of infant distress. This intervention is extended to the first 2 years of life to coincide with the duration of breastfeeding recommended by the WHO (see recommendation #6) and the panel's view that pain management should be consistent and comprehensive in early childhood to prevent unnecessary suffering and the potential for harm from unmitigated pain. Additional information regarding implementation of breastfeeding and topical anesthetics can be found in recommendations #6 and #17, respectively.

Oral Analgesics

Acetaminophen and ibuprofen are analgesics commonly administered in children and adults to treat fever and pain. They have been used in the context of vaccination in order to prevent and abort vaccine-induced fever and 'delayed' pain (i.e., pain occurring in the hours to days after vaccination)[159]. There is some controversy regarding their routine use to prevent and/or treat side effects of vaccination because of the potential to interfere with the immune response of some vaccines[160]. For the purposes of this guideline, a summary of the research evidence regarding the effectiveness of acetaminophen and ibuprofen specifically for reducing acute injection-related pain (rather than delayed pain) was reviewed.

20. Should acetaminophen be given before vaccine injections in individuals of all ages?
We suggest <u>against</u> giving acetaminophen before vaccine injections in individuals of all ages (weak recommendation, low confidence in estimates of effect).

No studies specific to vaccine injections were identified. One study including children aged 1 to 18 years with cancer undergoing needle insertion into a subcutaneously implanted port was included in the systematic review[161]. Children received either acetaminophen (40mg/kg) or placebo 1 hour prior to port access. There was low quality evidence for pain (critical outcome) due to indirectness and imprecision and no evidence of a benefit from this intervention: [n=26: SMD -0.64 (95% CI -1.43, 0.15)].

In addition to the above, 5 studies were identified that examined the potential for interference with the immune response (important outcome) with acetaminophen use prior to vaccination that are worthy of summary. Three studies including 442 adults receiving influenza vaccine demonstrated no difference in the immune response for those who received acetaminophen compared to placebo[162-164]. However, one study including 496 health care workers receiving hepatitis B vaccination series demonstrated a 26% reduction in hepatitis surface antigen antibodies in the acetaminophen group[165]. Another longitudinal study including 459 healthy infants following their primary and booster vaccination (10-valent pneumococcal non-typeable *Haemophilus influenza* protein D-conjugate vaccine, diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-*H influenzae* type b vaccine and rotavirus vaccine) demonstrated lower levels for all 10 pneumococcal vaccine serotypes, protein D, anti-diphtheria, anti-tetanus and anti-pertactin in the prophylactic acetaminophen group[160].The proposed mechanism for reduced immunogenicity is interference with the early interactions of the dendritic cells, T cells and B cells of the primary immune response to conjugate and toxoid vaccines via reduction of inflammatory signals at the injection site[160] .

Based on the results of the systematic review, acetaminophen is not recommended as pre-medication for reducing acute pain due to vaccine injections. The lack of analgesia observed in the included study is consistent with research in neonates undergoing heel lancing procedures[166].

While sweetening agents are included in the pharmaceutical formulation of acetaminophen which may confer some benefit in young children if administered immediately before vaccine injections (see recommendations #22 and #23), acetaminophen is not recommended to be used for this purpose; rather, sweet-tasting solutions should be used instead (see recommendations #22 and #23) or breastfeeding (see recommendation #6), particularly in light of the potential for acetaminophen to interfere with vaccine effectiveness.

These recommendations do not consider the effects of acetaminophen on reducing delayed pain or other adverse events occurring following immunization and other resources should be consulted for their appropriate management.

21. Should ibuprofen be given before vaccine injections in individuals of all ages?
We suggest <u>against</u> giving ibuprofen before vaccine injections in individuals of all ages (weak recommendation, very low confidence in estimates of effect).

No studies specific to vaccine injections were identified. One crossover trial including 10 adult volunteers undergoing venipuncture was included in the systematic review[167]. Adults received ibuprofen 5% cream and topical anesthetics (lidocaine-prilocaine 5% cream) 1 hour prior to venipuncture. There was very low quality evidence for pain (critical outcome) due to indirectness (procedure, route of administration of ibuprofen, and active comparison group) and imprecision, and no evidence of a benefit from this intervention. The results demonstrated more pain in the ibuprofen group compared to the lidocaine-prilocaine group: SMD 0.77 (95% CI 0.06, 1.48)].

No studies were identified that evaluated the effect of ibuprofen on immunization antibody response. Ibuprofen is an inhibitor of the cyclooxgenase enzyme and it is unclear whether blocking the metabolites of this enzyme system would interfere with vaccine effectiveness[168].

Based on the results of the systematic review, ibuprofen is not recommended as a pre-medication for reducing vaccine injection pain. While sweetening agents are included in the pharmaceutical formulation of ibuprofen which may confer some benefit in young children if administered immediately before vaccine injections (see also recommendations #22 and #23), ibuprofen is not recommended for this purpose. Sweet-tasting solutions should be used instead (see recommendations #22 and #23). As with acetaminophen, the effects of ibuprofen on delayed pain and other adverse events following immunization were not considered.

Sweet-tasting solutions

Sweet-tasting solutions (e.g., sucrose solutions and glucose/dextrose solutions) have been extensively evaluated for their analgesic and calming effects in infants undergoing needle procedures[169]. The mechanism of action of sweet-tasting solutions is not known but may involve release of endogenous opioids and distraction. Sweet-tasting solutions are commonly used in hospital settings to reduce distress in infants undergoing various types of aversive medical procedures[74,170].

The panel reviewed the effects of sucrose and glucose/dextrose solutions separately (recommendation #22 and #23, respectively). In addition, the effects of sweet-tasting solutions combined with other interventions (i.e., non-nutritive sucking and breastfeeding) prior to vaccine injection were reviewed (recommendations #24 and #25, respectively). Some data supporting co-administration of sweet-tasting solutions and sucking is present for other types of needle procedures[171].

22. Should sucrose solution be given before vaccine injections in children 0-2 years?
We recommend giving sucrose solution before vaccine injections in children 0-2 years (strong recommendation, moderate confidence in estimates of effect).

Eighteen studies were included in the systematic review including children in the first 19 months of life undergoing vaccine injections[17,75,86,97,102,172-184]. The sucrose concentrations evaluated ranged from 12% to 75% in all but one study, which described using a 'saturated' solution. The volume used was 2 mL in all but three studies (others used 0.75 mL or 0.6 mL/kg) and the usual timing of administration was 2 minutes prior to injection. The majority of studies included multiple separate vaccine injections. Across all distress measures (critically important outcome), the quality of evidence was high to moderate (due to imprecision). The results were positive for 4 out of 5 measures of distress. In the analysis including the largest number of studies (n=2071 participants), there was a benefit for distress in the acute and recovery phase combined: -0.76 (95% CI -1.19, -0.34). Sub-group analyses were undertaken for 3 of the distress outcomes; they suggest a dose-response relationship with concentrations above 20% sucrose (weight/volume) being the threshold for a benefit.

Implementation considerations:

Due to the observed benefit of sucrose solution on different markers of distress, sucrose solution is strongly recommended for the management of vaccination pain. This recommendation applies to children in the first 2 years of life who are not breastfed during vaccine injections (see recommendation #6). The upper age limit is a practical cut-off for this intervention given the trade-offs between potential benefits vs. harms and feasibility (fast onset of action, inexpensive, ease of administration) and is consistent with the recommendation regarding breastfeeding in young children (see recommendation #6).

The majority of studies administered 2 mL orally with a syringe within 2 minutes of vaccine injection(s). The volume is small, and consistent with other commonly administered medications. The volume and timing of administration relative to the procedure make this intervention feasible across different practice settings. The duration of action is not known; at present, the analgesic effect is believed to last about 5 minutes[169] (Harrison et al., 2012) although the calming effects may last considerably longer[185]. While this timeframe allows for multiple separate vaccines to be injected, a repeat dose may be administered, if needed.

Some infants may refuse to drink sucrose solutions or cough/spit up with its use. Alternatives to sucrose solution should be considered in the event that infants refuse to accept sucrose. Breast milk administered via a syringe ***before*** vaccine injections is not considered a substitute for sweet-tasting solutions. Limited data in neonates undergoing needle procedures suggest that breast milk is not as effective[73]. If breast milk is administered ***during*** vaccine injections in a bottle while holding infants it may simulate breastfeeding, which is effective (see recommendation #6).

For infants who are scheduled to receive oral rotavirus vaccine at the same time as injectable vaccines, sucrose solutions may not be necessary because rotavirus vaccine contains sucrose (as a flavouring agent) and has been demonstrated to have analgesic effects[186]. The sequence of vaccination could therefore be standardized to begin with rotavirus vaccine to achieve the added benefit of analgesia during administration of the injectable vaccines. It should be noted, however, that the only study to demonstrate an analgesic effect of rotavirus vaccine utilized a commercially available product with a high concentration of sucrose (71.5%) (Rotarix™)[186]. Rotarix is one of two rotavirus vaccines currently approved and recommended in Canada by the National Advisory Committee on Immunization (NACI) [http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-4/index-eng.php]; the other is RotaTeq.™ The concentration of sucrose in RotaTeq is 54%. Multiple vaccine formulations are available around the world which contain vastly different concentrations of sucrose (between 0.9% and 71.5%); it is not known whether the preparations containing lower concentrations of sucrose would be effective.

Oral analgesics (e.g., acetaminophen, ibuprofen), which also contain sweet-tasting flavouring agents, are not recommended as a substitute due to the potential for interference with the immune response[160] (see recommendations #20 and #21).

Sucrose solution is a treatment for vaccine injection pain only and is not a food. As such, it does not interfere with breastfeeding. The infrequency of vaccine injections (vs. eating) makes it unlikely that infants will learn to associate sucrose with pain and develop feeding aversion. The small volume and infrequent use of sucrose solution in this context prevent any harm to teeth (i.e., dental caries).

Resources are required to be able to implement this intervention, including: cost of sucrose and supplies for sucrose administration, and training of health care providers. Commercially available sucrose solution can be purchased by hospitals. Alternatively, sucrose solutions can be manufactured by clinicians practicing across practice settings, pharmacists and parents. If made by health care providers, there are some additional costs in terms of time and supplies. Sucrose solutions can be made by mixing table sugar with water (clean drinking water or boiled water). Use one packet of sugar (i.e. about one teaspoonful) mixed in 10 ml (i.e. two teaspoons) of water. The time and resources involved in using sucrose are considered minor. As they can become contaminated, it is recommended that either commercially available solutions or freshly made solutions be used. Sucrose solutions may be combined with non-nutritive sucking (see recommendation #24).

23. Should glucose solution be given before vaccine injections in children 0-2 years?
We recommend giving glucose solution before vaccine injections in children 0-2 years (strong recommendation, moderate confidence in estimates of effect).

Six studies investigating glucose (dextrose) for vaccine injections in infants in the first 12 months of life were included in the systematic review[77,89,187-190]. In included studies, the concentration of glucose ranged from 25% to 50% and the volume administered ranged from 1-2 mL. The timing of administration was variable. The majority of the studies administered glucose 2 minutes before injection. The remainder administered it immediately before or repeatedly 30 seconds before/during/10-30 seconds after. There was high to moderate quality of evidence across the critical outcomes of distress; the quality was downgraded due to risk of bias or imprecision. The results were mixed for different indicators of distress. In the only analysis that included all of the studies (n=818), there was a benefit of glucose on acute and recovery distress combined: SMD -0.69 (95% CI -1.03, -0.35).

Implementation considerations:

This recommendation is intended for children in the first 2 years of life who are not breastfed (see recommendation #6) or given oral sucrose solution (see recommendation #22). Glucose solution can be used as an alternative to sucrose solution when sucrose solution is unavailable. Sucrose is being prioritized over glucose because the evidence base for sucrose solution is more robust than for glucose. Consistent with the recommendation for sucrose solution, this recommendation includes children up to 2 years of age as a practical cut-off for this intervention, given the trade-offs between potential benefits vs. harms and feasibility of use.

The optimal timing relative to vaccine injection is not known; administration 2 minutes prior to vaccine injections is the most common way sweet-tasting solutions have been administered. Administration of glucose solution during and after the procedure may be associated with child refusal to accept the solution and/or gagging, due to crying. Administration after injection may also prevent parents from using other pain relieving interventions (e.g., holding interventions).

Alternative interventions should be considered in the event that infants refuse to drink glucose solution. Breast milk administered via a syringe ***before*** vaccine injections is not considered a substitute for sweet-tasting solutions; limited data in neonates undergoing needle procedures suggest that it is not as effective[73] (see recommendations #6 and #22).

Finally, oral rotavirus vaccine, which is co-administered with injectable vaccines in young infants, could be given prior to the injectable vaccines rather than glucose[186] (see also recommendation #22). A number of rotavirus vaccine formulations are available that contain sucrose (as a flavouring agent); however, their sucrose concentrations vary considerably (0.9% to 71.5%). To date, Rotarix,™ which contains 71.5% sucrose, has been shown to have analgesic properties[186].

The use of oral analgesics that contain sweet-tasting solutions (e.g., acetaminophen, ibuprofen) is not recommended as a substitute due to the potential for interference with the immune response[160] (see recommendations #20, #21).

Glucose solution is a treatment for vaccine injection pain only and is not a food. As such, there is it does not interference with breastfeeding. The infrequency of vaccine injections (vs. eating) makes it unlikely that infants will learn to associate sucrose with pain and develop feeding aversion. When used in this context, it is not expected to negatively impact on teeth (dental caries).

Commercially available glucose solutions are readily available in hospital settings. Parents do not have access to glucose solutions and clinicians would be required to provide it. The inconvenience to clinicians related to use of this intervention is considered minor. Glucose solutions may be combined with non-nutritive sucking (see recommendation #24).

24. Should sweet-tasting solutions (sucrose, glucose) be given before vaccine injections in combination with non-nutritive sucking (using a finger/thumb, pacifier) during vaccine injections (rather than sweet-tasting solutions or non-nutritive sucking alone) in children 0-2 years?
We suggest combining sweet-tasting solutions (sucrose, glucose) before vaccine injections and non-nutritive sucking (using a finger/thumb, pacifier) during vaccine injections in children 0-2 years (weak recommendation, very low confidence in estimates of effect).

One study including 74 infants aged 2 to 4.5 months undergoing vaccination was included in the systematic review that evaluated the combined effect of non-nutritive sucking and glucose solution vs. either alone[189]. There was very low quality evidence across critical outcomes (distress) due to risk of bias and imprecision. While the results demonstrated no evidence of a benefit of the combination of glucose and non-nutritive sucking for different indicators of acute and recovery distress, infants were held which could have made it more difficult to detect an added benefit. The SMD was -0.32 (95% CI -0.79, 0.15) and the RR was 0.99 (95% CI 0.78, 1.26), respectively for this outcome.

Implementation considerations:

While there was no evidence of a benefit of this intervention, it is being suggested for children in the first 2 years of life undergoing vaccinations that are not breastfed during vaccinations and engage in either thumb/finger-sucking or sucking on pacifiers. The rationale for this recommendation is that using both sweet-tasting solutions and sucking together may better simulate breastfeeding than either sweet-tasting solutions or sucking alone, and breastfeeding is the preferred method of pain relief in this population (see recommendation #6). There is also external evidence of an additive effect of combining sweet-tasting solutions and sucking in neonates undergoing needle procedures[100]. Using a pacifier or sucking on a finger/thumb is feasible for infants that already accept/use these methods and does not require additional resources. However, sucking may not occur at the right time. Additional resources are needed, however, to implement sweet-tasting solutions. These factors must be considered in the decision to use this intervention (see also related recommendations #12, #22, and #23).

25. 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 years?
We suggest against using breastfeeding and sweet-tasting solution (sucrose, glucose) combined together before vaccine injections in children 0-2 years (weak recommendation, low confidence in estimates of effect).

One study including 90 infants less than 3 months of age was included whereby breastfeeding and sucrose were both used ***before*** vaccine injections (breastfeeding first then sucrose) compared to either breastfeeding or sucrose alone[86]. The quality of evidence was low due to unclear risk of bias across several domains and imprecision and there was no evidence of a benefit: the SMD for acute distress was 0.28 (95% CI -0.34, 0.90) and the SMD for recovery distress was 0.06 (95% CI -0.37, 0.50).

The lack of observed benefit of this combination coupled with the inconvenience and added resources of using a sweet-tasting solution in a child who is already breastfeeding (breastfeeding is preferred over sweet-tasting solutions as a pain-relieving intervention for this age group – see also recommendations #6, #7, #22 and #23) led to a recommendation against it by the panel. This recommendation is directed to children in the first 2 years of life in order to maintain consistency with recommendations for breastfeeding and sweet-tasting solutions (see recommendations #6, #7, #22, and #23).

This recommendation does not preclude the administration of oral rotavirus vaccine (see recommendations #22 and #23) in combination with breastfeeding. The recommended order of

administration is rotavirus vaccine first then breastfeeding, if breastfeeding is performed during vaccination (see recommendation #6). Alternatively, breastfeeding first then rotavirus vaccine if breastfeeding is performed before vaccination (see recommendation #7).

Vapocoolants

Vapocoolants are volatile liquids applied on the skin right before the procedure that immediately reduce the temperature of the surface of the skin as they evaporate, resulting in a sensation of cold at the application site [191]. Vapocoolants may reduce pain by competing with the pain sensation or decreasing the velocity of neural impulse conduction[191]. In some individuals, however, the sensation of cold is itself painful and can increase attention to the impending pain of injection. The effectiveness of vapocoolants was examined separately for 3 age groups (i.e., 0-3 years, >3-17 years, and adults) due to the potential for differences in how the intervention may work.

26. Should vapocoolants be applied before vaccine injections in children 0-2 years?
We suggest against applying vapocoolants before vaccine injections in children 0-2 years (weak recommendation, low confidence in estimates of effect).

One study was included in the systematic review that evaluated the effectiveness of vapocoolants in 60 infants aged 2 to 6 months of age undergoing vaccination[192]. There was low quality evidence for the outcome of distress (critical outcome) due to risk of bias and imprecision, and no evidence of a benefit. The SMD for acute procedure distress was -0.44 (95% CI -0.96, 0.07).

This recommendation is directed to children 0-2 years due to similarities expected across this age range in the effects of the intervention. Some children may find application of vapocoolants uncomfortable, which can contribute to the pain experience. Furthermore children of this age would have difficulty communicating their discomfort and/or preferences for the intervention. There are other effective and safe pain treatments for this population that should be used instead, such as: breastfeeding, holding, and topical anesthetics (see recommendations #6, #9, and #17, respectively).

27. Should vapocoolants be applied before vaccine injections in children >3-17 years?
We suggest against applying vapocoolants before vaccine injections in children >3-17 years (weak recommendation, low confidence in estimates of effect).

Five studies including 268 children aged 2 to 12 years undergoing vaccination were included[152,193-196]. Vapocoolants were administered using various techniques (e.g., direct spray, application of a cotton ball sprayed with vapocoolant). There was low quality evidence for pain (critical outcome) due to risk of bias from inconsistent or lack of blinding and imprecision and there was no evidence of a benefit: [n=228: SMD -0.38 (95% CI -0.89, 0.13)]. Given the young age range of the participants across studies and validity of self-report in this age group is questionable[44,45], we also examined distress. There was low quality of evidence for both indicators of distress evaluated (i.e., pre-procedure and acute), and no evidence of a benefit on either.

Due to the lack of observed benefit, vapocoolants are not recommended for use in children. The results are being extrapolated to adolescents because a systematic review in a related context (venipuncture) that included children and adolescents demonstrated no evidence of a benefit of vapocoolants[191]. Use of this intervention may prevent the use of well-supported therapies such as topical anesthetics (recommendation #17) and falsely reassure individuals and onlookers that pain is being managed. Some children may find application of vapocoolants uncomfortable, which can

augment their pain experience. The cold sensation can focus attention on the procedure, further augmenting pain.

28. Should vapocoolants be applied before vaccine injections in adults?
We suggest that vapocoolants be applied before vaccine injections in adults (weak recommendation, low confidence in estimates of effect).

One study including 185 adults undergoing vaccination was included in the systematic review[197]. There was low quality evidence for the outcome of pain (critical outcome) due to risk of bias and imprecision; mixed results were observed for this outcome when measured over different time epochs. For acute pain, the SMD was -0.78 (95% CI -1.08, -0.48). For pain during the recovery phase, the SMD was -0.10 (95% CI -0.39, 0.19).

Implementation considerations:

Due to evidence of benefit on acute pain, this intervention is suggested in adults. In the previous HELPinKIDS CPG, vapocoolants were not recommended; however, the scope included children only[20]. The preference of individuals for this intervention should be taken into consideration before this intervention is implemented. Cold sensation from the application of vapocoolants can cause some individuals discomfort. While this adverse effect has not been well studied in the context of vaccine injections, in a separate meta-analysis of vapocoolants for adult venipuncture pain, the magnitude of benefit from their use for venipuncture pain management was offset by the magnitude of discomfort from their application[191]; hence, this trade-off requires consideration when implementing this intervention.

Vapocoolants are convenient to use – they are sprayed onto the injection site for several seconds immediately before vaccination. The cooling effect dissipates quickly (within one minute) and a repeat dose may be required if the vaccine has not yet been injected within this time frame. Some training is required for clinicians administering this intervention to ensure that the dose and timing are correct and to avoid side effects (e.g., discomfort from excessive cold sensation, frostbite, skin discoloration).

In Canada, vapocoolants are available for sale to institutions only (i.e., they are not available for sale to consumers directly). Several commercial multi-dose products exist, including: ethyl chloride and the combination of 1,1,2,3,3-pentafluoropropane and 1,1,1,2-tetrafuoroethane. Instructions are available from the manufacturer, Gebauer, for its products (Gebauer's Ethyl Chloride™ and Pain Ease™)[198,199].

iv. Psychological interventions (Thoughts and behaviours)

Providing a signal of an impending procedure

Communicating with individuals undergoing vaccination and signalling the impending procedure is a routine part of the vaccination process to try to minimize sudden movements and elicit coping strategies in individuals. Hence, providing guidance on what to say during this interaction is regarded as important. It has generally been recommended that when communicating about painful procedures, the use of language that is unnecessarily negative should be avoided. Specifically, use of threatening words to describe a painful experience can increase its threat value, which has been shown to reduce efficacy of other interventions, such as distraction[200,201]. Thus, rather than warning about the painful aspects of a procedure (e.g., "Here comes the sting"), it has been suggested that more neutral descriptions or prompts about the procedure (e.g., "Here I go") be used instead. Providing these more neutral messages may minimize attention to threatening aspects of the pain experience. It is important to note that providing a prompt for an impending procedure is not the same as saying that it will not hurt (see recommendation #30) and that it is also distinct from educating individuals about pain

management prior to the procedure and providing them with relevant information, including procedural and sensory aspects (see recommendation #49).

29. Should a verbal signal of the impending procedure be used (rather than a signal of impending pain) by clinicians before vaccine injections in individuals of all ages?

We suggest a verbal signal of the impending procedure be used (rather than a signal of impending pain) before vaccine injections in individuals of all ages (weak recommendation, very low confidence in estimates of effect).

Three studies including 391 adults undergoing venipuncture[202,203] or venous cannulation[204] were included in the systematic review. In all studies, individuals were given a verbal signal about the start of the procedure (i.e., neutral signal) or a signal about the pain (i.e., pain signal). Data were available for the critical outcome of pain but not fear. There was very low quality evidence due to risk of bias, indirectness, and imprecision. In the analysis including all 3 studies (n=391), there was no evidence of a benefit: SMD -0.6 (95% -1.37, 0.16). However, pain scores were lower in the study by Vijayan et al., 2015[203] compared to the other included studies, suggesting lower pain perception in this patient population. When the data from this study were removed, there was a benefit of neutral verbal signalling (n=199): SMD 0.97 (95% CI -1.26, -0.68). In an analysis including two of the studies whereby pain was dichotomized, the RR was 0.29 (95% CI 0.01, 5.83); this analysis, however, included the study by Vijayan et al., 2015[203].

Implementation considerations:

The panel suggested using neutral verbal cues to signal impending vaccination across all ages. The rationale is that neutral language is less anxiety-provoking. While this may be more important for individuals who report higher levels of pain, as was demonstrated in the meta-analysis, there is no rationale for not using the same approach in individuals who report low levels of pain. Separately, it has been demonstrated that threatening words undermine pain-relieving interventions[200,201]. It should be noted that there is the potential for even very young children to understand what is being said and to experience increased distress as a result. Also, when saying that something is going to hurt, nonverbal signs (e.g., vocal tone, facial expression) of distress are more likely to be present while delivering the message than when saying something in a neutral manner, which may influence the responses of young children even if the words themselves are not understood. Parents may also respond to such words with increased anxiety which can be sensed by young children.

Individual differences may affect the success of this intervention. For example, an individual who is highly anxious may be more vigilant in the context of a needle procedure and thus providing a signal that the procedure is about to begin may be unnecessary and potentially heighten his/her distress, or be perceived as helpful. Alternatively, if one would like to disengage (i.e., remove attention) from the procedure, providing a signal of an impending procedure may undermine the individual's self-selected coping strategy. Individuals can be asked about their preferences. The interaction between individual differences and the success of this intervention is a topic worthy of future research.

Using suggestion

In general, suggestion is a psychological intervention that aims to alter the processing and interpretation of pain caused by vaccination by providing cognitive information that de-emphasizes the negative aspects of the painful procedure. For example, the individual is told that an intervention will make the vaccine hurt less. The panel distinguished between different types of suggestion. *False* suggestion was defined as messages of minimal pain (e.g., "it's just a poke") or untruths (e.g., "it won't hurt"). False suggestion may promote distrust between any individual delivering such messages and individuals undergoing vaccination[153]. *True* suggestion, on the other hand, was defined as messages

that are accurate, honest and not overstated or otherwise misleading. True suggestions are often used when educating about pain-relieving interventions and provide information that is consistent with evidence (see also recommendation #49). Suggestion that is combined with relaxation is referred to as hypnosis; hypnosis was not considered in the guideline as it is a more complex psychological intervention and not deemed feasible for implementation by clinicians involved in administering vaccine injections.

30. Should false suggestion be used during vaccine injections in individuals of all ages?
We suggest <u>against</u> using false suggestion during vaccine injections in individuals of all ages (weak recommendation, low confidence in estimates of effect).

Two studies including children aged 4 to 6 were included in the systematic review[195,205]. In both studies, children were given a placebo intervention (i.e., wearing headphones or air sprayed on the skin at the injection site) and told by the experimenter or clinician that something was being done to help them during the vaccine injection or to make the vaccine injection hurt less. Both studies examined the impact of adding suggestion to another intervention (i.e., distraction or vapocoolant spray) as well. There was low quality evidence for the critical outcome (pain) due to risk of bias and imprecision and no evidence of a benefit on pain (n=240 participants): SMD -0.21 (95% CI -0.47, 0.05). Since the inclusion of pain-relieving interventions with suggestions confounds the issue (i.e., there may have been some truth in the suggestion), the analysis was repeated excluding the data for pain-relieving interventions. The results were not altered: [n=140: SMD -0.24 (95% CI -0.59, 0.11)]. There was no evidence for the critical outcome of fear.

The use of language that is falsely reassuring or dishonest is not beneficial and may harm by decreasing trust. This recommendation is therefore being generalized to any individual who could deliver such messages (e.g. clinicians, parents, teachers) and individuals of all ages undergoing vaccination. Even if the individual is unable to understand the message (e.g., infant), onlookers (e.g., parents) that hear these messages may also be adversely affected (i.e., become distrustful).

<u>Using reassurance</u>

Health care provider and onlooker (e.g., parent) behaviours during stressful medical procedures can impact an individual's pain. Reassurance, which is a behaviour often used with the intention of reducing anxiety, has been demonstrated to be positively correlated with child distress and pain in observational and experimental studies during a variety of different procedures[206]. Examples of reassuring statements include: "It'll be over soon" and "You're ok". In terms of mechanism of action, there is evidence that children perceive adults to be worried when they reassure[207], thereby serving as a signal of threat. Reassurance may also focus the child's attention on the pain and increase distress or provide permission (i.e., act as a cue) for the child to show the distress he/she is already feeling[206]. For individuals with heightened fear and anxiety, reassurance may be particularly ineffective as it may simply lead to wanting more reassurance without a lasting reduction in fear (i.e., perpetuate "reassurance-seeking"[208-211].

31. Should repeated reassurance be used during vaccine injections in individuals of all ages?
We suggest <u>against</u> using repeated reassurance during vaccine injections in individuals of all ages (weak recommendation, very low confidence in estimates of effect).

Two studies[212,213] including children aged 3 to 7 years undergoing vaccination were included in the systematic review. In both studies, repeated reassurance by the parents was examined. Methods of training the parents in the use of reassurance varied between studies and included instructions, audio

and live modeling, and practice; parents were also reminded throughout the procedure to use reassurance. There was low to very low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was no evidence of a benefit of reassurance on critical outcomes. The SMD for pain (n=28 participants) was -0.18 (95% CI -0.92, 0.56) and the SMD for fear (n=54 participants) was -0.18 (95% CI -0.71, 0.36). Given the young age range of the participants and that validity of self-report in this group is questionable[44,45], we also examined distress; there was very low quality of evidence for distress (important outcome) and no evidence of a benefit.

This recommendation applies to individuals of all ages. There is strong rationale across childhood for avoiding repeated reassurance as it is not generally helpful or even maladaptive[206,214-216]. Excessive use of reassurance may replace other more effective methods of comforting children during vaccine injections and signal threat to the individual undergoing vaccination. Even in infants, reassurance is associated with increased distress (while young infants do not necessarily understand the words being said, they may respond to other cues like vocal tone in which the messages are delivered and accompanying facial expression). There is rationale to extend this recommendation to adults as repeatedly saying statements like 'don't worry it will be over soon' are expected to be at least not helpful and potentially anxiety-provoking; in fact, ineffective use of reassurance with adults is problematic in longer-lasting pain and other health contexts[209,217-220]. Some forms of reassurance may be more helpful than others[206,207,216]; however, further research is needed to elucidate these details. Health care providers and parents are encouraged to carefully observe the individual being vaccinated and to be responsive and sensitive to his/her cues as this recommendation only applies to simplistic repeated reassurance and providing some reassurance is typical behavior of both health care providers and parents during vaccine injections. The included studies tested the effects of training parents to *repeatedly* (or excessively) provide reassurance during vaccine injections.

Distraction

Distraction involves the use of strategies to divert an individual's attention away from pain to something more pleasant[221]. Distraction may reduce pain by engaging neural mechanisms that facilitate endogenous modulation of pain[222,223] as well as decreasing attentional resources that would otherwise be allocated to pain processing[224]. Distraction can be achieved using a variety of 'distractors'. In children, this typically includes toys, videos, and music. However, distraction can also involve conversation with an adult. Distractors that are very engaging, interactive, and intrinsically interesting have been postulated to be more effective[221,225]. Distraction is typically commenced before the procedure begins, and is continued during and afterwards - this is believed to reduce anticipatory apprehension/fear, pain, and to enhance recovery, respectively[225]. Recent systematic reviews of the effects of distraction in children demonstrate a benefit of distraction when used to reduce pain during various needle procedures, including vaccination[226-228].

It is important to note that from birth, individuals develop increasing intentionality and control in their self-regulatory processes related to distress regulation. Throughout development, children become less reliant on external sources of distraction to cope with pain[229,230]. Distraction varies from being completely dependent on another person ("directed distraction", e.g., an infant having his/her attention directed away from the painful sensation by a caregiver's use of a rattle) to entirely self-regulatory ("non-directed", e.g., an adult using imagery with no direction from another needed). Importantly, however, an infant may be able to independently direct his/her attention away from a painful stimulus (e.g., through the availability of a musical mobile) and for an older individual, his/her attention can be directed away from a painful stimulus by another individual.

There may be substantial individual differences in the effectiveness of distraction for pain reduction[231] due to individual coping style. Distraction may be more effective for individuals whose

typical coping style involves disengaging[200,232,233] rather than attending to the source of pain and also for those who have a low fear of pain[201].

To account for potential differences in the effects of distraction according to developmental stage, we maintained separation in the analyses between four age categories: birth to 3 years, >3-12 years, >12-17 years, and adult. In general, the literature did not substantiate subgroup analyses focusing on whether the distraction was directed versus non-directed. The one exception to this was in younger children (0-3 years). Given the steep trajectory of development in self-regulation in young children and the availability of relevant literature, subdivisions of directed versus non-directed were incorporated into the analyses of the efficacy of distraction in children less than three years old. Across ages, distraction interventions were subdivided according to type (e.g., toy, video, music, verbal) and analyzed separately.

32. Should directed video distraction be used during vaccine injections in children 0-3 years?
We suggest directed video distraction be used during vaccine injections in children 0-3 years (weak recommendation, very low confidence in estimates of effect).

Four studies including children aged 1 month to 3 years were included in the systematic review[144,234-236]. In three of the studies, nurse immunizers were instructed in distraction prior to commencement of the study[144,234,235] and in one of the studies, parents were also instructed in distraction [235]. In all included studies, children were encouraged to engage in the distraction. There was moderate to very low quality evidence for the critical outcomes of distress due to imprecision, with or without risk of bias. The results were mixed; there was evidence of a benefit for pre-procedural distress [n=216: SMD -0.49 (95% CI -0.76, -0.22)] and distress during the acute and recovery phases combined [n=126: SMD -0.68 (95% CI -1.04, -0.32)]. In the analysis including the largest number of studies (n=456), there was no evidence of a benefit for acute distress: SMD -0.63 (95% CI -1.53, 0.27).

<u>Implementation considerations</u>:

The panel considered various factors in its decision to suggest this intervention, including: 1) observed benefit for some measures of distress, and 2) feasibility of this intervention (availability of electronic video devices in vaccination settings or, increasingly, personal devices used by parents such as smartphones).

It should be noted, however, that this intervention could interfere with or inappropriately replace other more effective methods of reducing pain in children during vaccine injections (e.g., see recommendations #9, #17, #22). There is also the potential for variability in the intervention implementation (type of video, timing of use relative to procedure, behaviour of individual carrying out the intervention) that could lead to a lack of benefit, and possibly even increase child distress. The developmental needs of children across this age range should be considered. In particular, it has been established that one of the core developmental needs of an infant in distress is close proximity to caregiver (i.e., holding child close)[95,237] (see recommendation #9); if the current recommendation to use directed video distraction is implemented incorrectly, it could interfere with the child's ability to achieve this core developmental need.

Additional research is recommended to determine whether aspects of the intervention (type of video), its delivery (timing of use relative to procedure), and child factors (ages/developmental) influence effectiveness (see also recommendations #33 and #34). A review of video distraction in >3-12 year old children is available in recommendations #36.

33. Should directed toy distraction be used during vaccine injections in children 0-3 years?
We suggest directed toy distraction be used during vaccine injections in children 0-3 years (weak recommendation, very low confidence in estimates of effect).

Five studies including children aged 2 months to 3 years undergoing vaccination were included in the systematic review[236,238-241]. In three of them, parents were instructed in distraction. There was low to very low quality evidence across the critical outcome of distress due to risk of bias and imprecision. The results were mixed; a benefit was demonstrated for distress in the pre-procedure, acute and recovery phases combined in one study [n=81: SMD -0.47 (95% CI -0.91, -0.02)]. In the only analysis that included all 5 studies (n=549), there was no evidence of a benefit for acute distress: SMD -0.94 (95% CI -1.98, 0.10).

Implementation considerations:
The rationale and applicability considerations for this recommendation are similar to recommendation #32.

34. Should non-directed toy distraction be used during vaccine injections in children 0-3 years?
We suggest non-directed toy distraction be used during vaccine injections in children 0- 3 years (weak recommendation, very low confidence in estimates of effect).

Four studies including children aged 2 months to 3 years undergoing vaccination were included in the systematic review[141,238,241,242]. The methods of distraction included toys and mobiles. There was low to very low quality of evidence due to risk of bias and imprecision for the critical outcome (distress) and the results were mixed for different indicators of distress. In the only analysis that included all 4 studies (n=290), there was a benefit for acute distress: SMD -0.93 (95% CI -1.86, 0.00).

Implementation considerations:
The rationale and applicability considerations for this recommendation are similar to recommendation #32.

35. Should verbal distraction be used during vaccine injections in children >3-12 years?
We suggest verbal distraction be used during vaccine injections in children >3-12 years (weak recommendation, low confidence in estimates of effect).

Two studies investigated verbal distraction in children aged 3 to 7 years undergoing vaccination[212,243]. Parents were instructed in verbal distraction using a pamphlet, or by oral instruction plus listening to a tape and practicing. Parents then distracted their children by talking to them, counting, singing, discussing other objects in the room, reciting a poem/rhyme, or other. There were no studies that examined verbal distraction provided by a clinician. There was low quality evidence due to risk of bias and imprecision for one of the critical outcomes (pain) and no evidence for the other (fear). There was no evidence of a benefit on pain (n=28): SMD -0.27 (95% CI -1.02, 0.47). Given the young age range of the participants and that the validity of self-report in this age group is questionable[44,45], we also examined distress; there was low quality of evidence for distress (important outcome) and evidence of a benefit: [n=46: SMD -1.22 (95% CI -1.87, -0.58)].

Implementation considerations:
This intervention is suggested for children >3-12 years as it is reasonable to believe that the intervention could have some benefit across this age range and because of the feasibility of this

intervention across different vaccination settings. The evidence base does not include administration of the intervention by clinicians, who may be more effective than parents[244].

We note, however, that there is potential for wide variability in the implementation of this intervention (e.g., due to differences in behaviours of individuals directing the verbal distraction) and that the developmental needs of children across this age range may impact on effectiveness of the intervention. Parents who are distressed themselves may not be able to successfully distract their child on their own or may require additional training or support; their child may also benefit more from clinician-led distraction, particularly if the child is (or is expected to be) highly distressed[245,246]. The use of this intervention should not preclude the use of other effective interventions (for example, see recommendation #17) and individual preferences should be taken into account. Additional research is recommended for this intervention, particularly when administered by clinicians and for populations not included in the current evidence base (e.g., adolescents and adults).

36. Should video distraction be used during vaccine injections in children >3-12 years?
We suggest video distraction be used during vaccine injections in children >3-12 years (weak recommendation, very low confidence in estimates of effect).

Five studies including children aged 2 to 12 years were included in the systematic review[143,196,247-249]. Nurse immunizers, parents and/or children received verbal, written or video instruction in distraction in 2 of the studies[143,248] and children typically watched a cartoon or movie on a television. There was very low quality evidence for critical outcomes (pain and fear) due to risk of bias and imprecision. There was no evidence of a benefit for pain [n=279: SMD -0.88 (95% CI -1.78, 0.02)] or fear [n=68: SMD 0.08 (95% CI -0.25, 0.41)]. When the single study that allowed the child to choose from several available videos[248] was examined separately, a benefit of video distraction was observed for pain: [n=92: SMD -2.24 (95% CI -2.79, -1.68)]. Given the young age range of the participants and that the validity of self-report in this age group is questionable[44,45], we also examined distress. There was very low quality of evidence for distress and evidence of a benefit across all three distress indicators assessed. In the analysis including all 5 studies (n=327), the SMD was -0.96 (95% CI -1.85, -0.08).

Implementation considerations:

The panel suggests video distraction despite the lack of demonstrated benefit across all critical outcomes. Firstly, there was a consistent benefit on distress. Secondly, the intervention is feasible across various vaccine settings. Thirdly, there are a variety of newer technology products (e.g., smart phones) available that may be more engaging than the older technology (e.g., DVD players) utilized in the included research. While it is postulated that child choice of video and interactivity are both factors that enhance effectiveness[221,250], this is not clearly supported by the cumulative research evidence[226] and further research is recommended.

Children and/or families are often in possession of these types of technologies and if not, the resources required to acquire them for widespread use are considered justified. Some brief training (e.g., < 5 minutes) may be required; the inconvenience is considered minor. The use of this intervention should not preclude the use of other more effective interventions (for example, see recommendation #17) and individual preferences should be taken into account. A review of the evidence for this intervention in young children (0-3 years) is available in recommendation #32.

Specific data are lacking for adolescents. Research is recommended for this population as the use of electronic video devices is highly prevalent, making this a feasible intervention, particularly for school-based immunizations.

37. Should music distraction be used during vaccine injections in children >3-12 years?
We suggest music distraction be used during vaccine injections in children >3-12 years (weak recommendation, low confidence in estimates of effect).

Four studies including children aged 3 to 7 years undergoing vaccination were included in the systematic review[205,251-253]. In three of the studies, the music was delivered via headphones. There was low quality evidence due to risk of bias and imprecision. There was evidence of a benefit for pain: [n=361: SMD -0.45 (95% CI -0.71, -0.18)]. There was no evidence for the critical outcome of fear.

Implementation considerations:

The panel considered two primary factors in its decision to suggest this intervention: evidence of benefit and feasibility across different vaccination settings. Music interventions are easily implemented if children listen to their own music devices using ear/headphones. Additional resources may be required if children/families do not have their own supplies. A selection of developmentally appropriate music should be made available for the children to choose from to ensure that is enjoyable and of interest to them.

The use of this intervention should not preclude the use of other effective interventions (for example, see recommendation #17) and individual preferences should be taken into account. The effectiveness of alternative methods of delivery of this intervention (e.g., live music, drumming, and/or singing) is not known, and worthy of future research due to ease of implementation across vaccination settings. A review of the evidence for this intervention in adolescents and adults can be found in recommendations #38 and #39, respectively.

38. Should music distraction be used during vaccine injections in adolescents >12-17 years?
We suggest against using music distraction during vaccine injections in adolescents >12-17 years (weak recommendation, low confidence in estimates of effect).

One study including adolescents 13 to 15 years undergoing vaccination was included in the systematic review[254]. Adolescents listened to music using headphones. There was low quality evidence due to risk of bias and imprecision and no evidence of a benefit: [n=118: SMD -0.04 (95% CI -0.42, 0.34). There was no evidence for the critical outcome of fear.

While an attractive intervention due to feasibility (adolescents can use personal electronic devices), particularly for school-based vaccinations, the panel recommended against the use of this intervention due to the lack of demonstrated benefit and concern that this intervention would be used instead of other evidence-based interventions (e.g., recommendation #18). Importantly, the lack of analgesia observed in the included study is consistent with research including adolescents in related contexts (e.g., venipuncture)[226]. It is possible that adolescents involved in the study were not sufficiently engaged in the music distractors selected to derive benefit, that directing them to use an external distractor may have interfered with their preferred coping strategies, and/or that it does not add anything beyond what they may have already been doing (e.g., cognitive distraction). Furthermore, individuals may be less likely to rely on distraction to cope when a stressful situation is perceived to be controllable. The effectiveness of music distraction for younger children (>3-12 years) and adults is reviewed in recommendations #37 and #39, respectively.

39. Should music distraction be used during vaccine injections in adults?
We suggest <u>against</u> using music distraction during vaccine injections in adults (weak recommendation, very low confidence in estimates of effect).

No studies were identified specific to vaccine injections. Two studies including 156 adults undergoing venipuncture were included in the systematic review[255,256]. In both studies, individuals self-selected the music from a variety of options. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for both critical outcomes. The SMD for pain was -0.10 (95% CI -0.48, 0.27) and the SMD for fear was -0.25 (95% CI -0.61, 0.10).

Due to the lack of benefit, this intervention is not recommended. It is possible that the individuals involved in the studies were not sufficiently engaged in the music distractors selected to derive benefit, that directing adults to use an external distractor may have interfered with their preferred coping strategies[257], and/or that it does not add anything beyond what they may have already been doing (e.g., cognitive distraction). Furthermore, individuals may be less likely to rely on distraction to cope when a stressful situation is perceived to be controllable. Given the prevalence of some degree of needle fear is estimated at between ~15-38% in adults[6,8,9,11,258,259], the majority may perceive a vaccination to be minimally stressful and may consider it within their general abilities to cope with the pain. The exception to this is for adults with significant levels of needle fear.

This intervention should not replace more effective methods of pain control during vaccine injections in adults, such as topical anesthetics (recommendation #18). A review of the available evidence for this intervention in children >3-12 years and adolescents >12-17 years is available in recommendations #37 and #38, respectively.

40. Should visual distraction be used during vaccine injections in adults?
We suggest <u>against</u> using visual distraction during vaccine injections in adults (weak recommendation, very low confidence in estimates of effect).

No studies were identified specific to vaccine injections. Two studies including adults undergoing venipuncture were included in the systematic review[256,260]. A kaleidoscope was used as the distractor in both studies. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for either. Both studies were included in the analysis of pain (n=177 participants) and the resulting SMD was -0.57 (95% CI -1.82, 0.68). Only one study[256] had data for the critical outcome of fear (n=81): the SMD was -0.05 (95% CI -0.50, 0.40).

Due to the lack of benefit of this intervention, it is not being recommended. The results are supported by an excluded study whereby distraction (using a self-selected magazine article) during vaccination was demonstrated to be inferior to topical anesthetics[261] on self-reported pain. As described in recommendation #39 (above), it is possible that the individuals involved in the studies were not sufficiently engaged in the visual distractor selected to derive benefit, that directing adults to use an external distractor may have interfered with their preferred coping strategies, that it does not add anything beyond what they may have already been doing (e.g., cognitive distraction), and/or that pain is considered minimally painful and frightening. Effective methods of pain control should be offered (e.g., recommendation #18).

Breathing interventions (including blowing, coughing, breath holding and deep breathing)

Breathing interventions have been proposed to reduce pain during medical procedures. A variety of techniques have been studied, including: breathing with or without a toy distraction, deep breathing, coughing, and forceful breath-holding (or exhalation). Breathing facilitated with toy distractors typically includes blowing bubbles or blowing on pinwheels and is used with children. Deep breathing (i.e., belly or diaphragmatic breathing) is another breathing intervention which is associated with relaxation and often included in cognitive-behavioural treatments for pain[228,262,263]. The panel examined the evidence base for specific breathing interventions according to age domain, as relevant, to account for potential differences in the types of interventions and effectiveness: children >3-12 years, adolescents >12-17 years and adults (recommendations #41, #42, #43, #44).

41. Should breathing with a toy distraction (e.g., blowing bubbles, pinwheels) be used during vaccine injections in children >3-12 years?

We suggest breathing with a toy distraction (e.g., blowing bubbles, pinwheels) be used during vaccine injections in children greater >3-12 years (weak recommendation, very low confidence in estimates of effect).

Six studies including children aged 3 to 9 years undergoing vaccination were included in the systematic review[110,213,264-267]. In three of them, parents and children received instruction prior to the procedure. A variety of props were used to facilitate breathing, including: bubbles, pinwheels, and responding to a robot's request to blow dust off a toy. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was evidence of a benefit for pain [n=123: SMD -0.49 (95% CI -0.85, -0.13)]. There was no evidence of a benefit for fear. Given the lower age range of the participants and that reliance on self-report may be problematic[44,45], the effects of the intervention on distress were also examined. There was very low quality evidence and evidence of a benefit for distress measured in the acute procedure phase and distress measured during the pre-procedure, acute and recovery phases combined. For the analysis of pre-procedure, acute and recovery distress combined, which included the largest number of studies (n=222 participants), the SMD was -0.55 (95% CI -0.82, -0.28).

Implementation considerations:

The intervention is suggested for children >3-12 years due to evidence of benefit and feasibility across vaccine settings. Some resources may be required to instruct individuals and to have suitable toys available; however, these are minor.

42. Should breathing without a toy distraction (blowing, deep breathing) be used during vaccine injections in children >3-12 years?

We suggest against breathing without a toy distraction (blowing, deep breathing) during vaccine injections in children >3-12 years (weak recommendation, very low confidence in estimates of effect).

Two studies including children aged 3 to 7 years were included in the systematic review[268,269]. In both studies, children were instructed in breathing exercises prior to vaccinations. In one study[269], children watched a video introducing "snake breathing" where they are instructed to breathe deeply with a hissing sound. Introducing breathing in this way may have helped to make the strategy more concrete/clear and interesting; however, it was also potentially fear-inducing. The video also taught children about positive self-statements (i.e., "I am cool and calm") and showed a child modeling these strategies. In the second study[268], children were instructed to take a deep breath and blow and blow and blow until they were told to stop. There was very low quality evidence for critical outcomes (pain and

fear) due to risk of bias and imprecision and no evidence of a benefit. The SMD for pain (n=136) was -0.27 (95% CI -0.61, 0.07) and the SMD for fear (n=61) was -0.36 (95% CI -0.86, 0.15). There was very low quality of evidence for distress (important outcome) and no evidence of a benefit.

This intervention is not recommended due to the lack of a benefit. It is unclear to what degree deep breathing was incorporated in the reviewed studies (rather than simplistic blowing). Use of this intervention may inappropriately replace other more effective pain treatments (e.g., recommendation #17). Alternative effective distraction interventions can be employed (e.g. recommendation #41).

43. Should breathing interventions (cough) be used during vaccine injections in children >3-17 years?

We suggest <u>against</u> breathing interventions (cough) during vaccine injections in children >3-17 years (weak recommendation, low confidence in estimates of effect).

One study including 136 children 4 to 13 years was included in the systematic review[270]. Children were asked to cough during vaccination. There was low quality evidence due to risk of bias and imprecision. There was no evidence of a benefit on pain, one of the critical outcomes and no data for fear, the other critical outcome. The SMD for pain was -0.17 (95% CI -0.41, 0.07).

This intervention is not recommended due to the lack of a benefit. Use of this intervention may inappropriately replace other more effective pain treatments (e.g., recommendations #17 and #18). The effectiveness of this intervention in adults is reviewed in recommendation #44.

44. Should breathing interventions (cough, breath-hold) be used during vaccine injections in adults?

We suggest breathing interventions (cough, breath-hold) be used during vaccine injections in adults (weak recommendation, very low confidence in estimates of effect).

No studies were identified specific to vaccine injections. Two studies including 138 adults undergoing venipuncture were included in the systematic review[271,272]. In one study, participants coughed during the procedure[272]. In the other, participants were asked to perform a deep inspiration and then hold their breath[271]. There was very low quality evidence for the critical outcome of pain due to risk of bias, indirectness and imprecision. There was evidence of a benefit for pain: SMD -0.82 (95% CI -1.21, -0.43). There was no evidence for the critical outcome of fear.

<u>Implementation considerations</u>:

This intervention is being suggested for use as there is evidence of a benefit and the intervention is feasible across vaccine settings. Some resources may be required to instruct clinicians in the use of this intervention as they are required to direct individuals undergoing vaccination to perform these breathing manoeuvres; however, this is considered minor.

<u>v. Process interventions</u>

Effective implementation of treatments for pain during vaccine injections require that different stakeholders involved in vaccination are present, willing to use them, adequately trained and supported. These stakeholders include: clinicians administering vaccinations, parents of children undergoing vaccination, and individuals undergoing vaccination. Different methods of education for key individuals involved in vaccination have been evaluated in different vaccination settings. Education has been provided both prior to and on the day of vaccination. The panel considered the effect of parent presence during vaccination of children and educational interventions aimed at different populations;

clinicians administering vaccine injections, parents of children undergoing vaccinations and individuals undergoing vaccinations (see recommendations #45-49).

Education of clinicians

Clinicians (physicians, nurses, pharmacists) routinely provide education about vaccinations and interventions for mitigating pain during vaccination and should therefore be knowledgeable about evidence-based approaches. Clinicians administering vaccinations are required to be additionally competent in vaccine administration techniques, which include techniques to minimize pain. Individuals receiving vaccinations value efforts made by clinicians to minimize pain as it demonstrates that clinicians are competent and that they care about them [153]. Current national vaccination resources, such as the Canadian Immunization Guide[51] and the Red Book[49] include guidance about managing pain during vaccine injections. The panel evaluated the effectiveness of educating clinicians administering vaccinations about interventions for pain (recommendation #45).

45. Should clinicians administering vaccine injections be educated about vaccine injection pain management?

We recommend education of clinicians administering vaccine injections about vaccine injection pain management (strong recommendation, low confidence in estimates of effect).

One study involving 53 public health nurses delivering vaccinations to children was included in the systematic review[273]. Public health nurses in the intervention group were trained in a variety of evidence-based pain treatments using a multi-faceted approach: 2-hour in-person education session including; a power-point presentation and practice scenarios delivered by a nursing manager, and online support. The control group did not receive this education. There was low quality evidence for the critical outcome (use of pain interventions) due to risk of bias. There was an increase in the use of pain interventions in the training group: [n=459: SMD 0.66 (95% CI 0.47, 0.85)] (N.B. better indicated by higher values).

Implementation considerations:

This recommendation involves all clinicians delivering vaccine injections. The panel values the use of techniques to minimize pain by clinicians administering vaccine injections in order to fulfill their ethical obligation to reduce unnecessary suffering and to demonstrate competency regarding best practices for vaccine injections. Additional resources are required to educate and support clinicians to be able to implement pain interventions. These resources are considered justified and are aligned with competencies for immunizers and immunization best practices, which include pain management competency. Education can be built into existing training and continuing education programs.

Of note, additional data demonstrating support for clinician education can be extracted from clinical questions for individual pain treatments whereby clinicians were instructed and involved in administering the interventions.

Parent presence

Children are vaccinated in different practice settings and parents often have the option of being present or absent (e.g., for vaccinations delivered in public health clinics, general practitioner offices). Family-centred health care promotes the inclusion of family members whenever possible[274].

46. Should parents be present during vaccine injections in children 0-10 years?
We recommend parental presence during vaccine injections in children 0-10 years (strong recommendation, very low confidence in estimates of effect).

Four studies including 245 children aged 13 months to 9 years were included in the systematic review[243,275-277]. Parents were present (and were not provided with any training on how to behave) or absent during their children's vaccinations. There were no data for the critical outcomes of pain and fear. There was very low quality evidence for distress (considered due to the inclusion of children unable to provide self-report or whereby self-report may be unreliable) due to risk of bias and imprecision. Extensive selective reporting bias, lack of blinding and a small sample size contributed to the quality rating. Results were mixed for different indicators of distress. There was a benefit of parent presence in the pre-procedure phase in 2 studies included in the meta-analysis (n=67): SMD -0.85 (95% CI 1.35, -0.35). Conversely, child distress was higher in the parent presence group during other phases of the procedure.

In one study, children showed a strong preference to have their parents present (important outcome)[276].

Implementation considerations:

The panel strongly recommended parent presence for several reasons: 1) children demonstrate higher levels of distress when parents leave (before vaccine injections), 2) children prefer to have their parents present during vaccine injections, and 3) this intervention is standard practice in young children and promotes family-centred care. Young children report high levels of needle fear[6] and having parents there may help them to feel more secure and supported.

Higher child distress during and after vaccination in the presence of parents may reflect stronger pain signalling by the child in order to engage parents (i.e., a normative response to distress in the absence of pain mitigation interventions) rather than a negative impact of parent presence per se. Nevertheless, education of parents is also recommended regarding about how to effectively comfort their children as parent behaviours can influence children's experiences of pain and fear (i.e., what parents *do* while present is critical to child outcome; see also recommendations #31, #35, #47 and #48). For parents who have been observed to struggle or become highly distressed in this situation, education is particularly important. These resources are considered justified to support family-centred care. Currently, resources have been incorporated into an immunization *app* distributed to the public by Immunize Canada free of charge to the public (http://immunize.ca/en/app.aspx)[22].

We are not confident in the values and preferences of older children (> 10 years) with respect to this particular intervention. They were not included in the evidence base and routinely undergo vaccination in school-based vaccination clinics in the absence of their parents. We additionally note that in some jurisdictions, children < 10 years of age may undergo vaccinations in the absence of their parents and implementation of this recommendation may be difficult. Provision of other measures and context-specific factors may mitigate the impact of not having parents present.

Education of parents of children undergoing vaccinations

Parents are concerned about pain during vaccine injections undertaken in their children and indicate a desire for education on pain and related issues[6,18,19,278]. If educated about evidence-based interventions, there is the potential for parents to use and advocate for use of these interventions during vaccine injections. To date, research has focused on the impact of providing parents with education either ahead of time or on the day of vaccination. These studies will be summarized below (recommendations #47 and #48, respectively).

47. Should parents be educated about vaccine injection pain management prior to the day of vaccination (i.e., ahead of time)?

We recommend education of parents about vaccine injection pain management prior to the day of vaccination (i.e., ahead of time) (strong recommendation, low confidence in estimates of effect).

Five studies were included in the systematic review that evaluated education of 589 parents of children less than 2 years of age prior to the day of vaccination[24,25,239,279,280]. In included studies, parents were trained in a variety of evidence-based pain treatments using different techniques, including: verbal instruction, pamphlets, and videos. Training took place in the hospital during prenatal classes or after delivery of an infant, and at outpatient clinics. These methods are consistent with usual methods and settings of education of the public about immunization. There was moderate to low quality of evidence across different indicators for use of pain interventions (critical outcome) due to risk of bias and imprecision with mixed results. In the analysis that included the largest number of studies (n=300 participants), there was a benefit on use of pain interventions: RR 2.08 (95% CI 1.51, 2.86) (N.B. better indicated by higher values). There was low quality evidence for distress in the children (critical outcome) due to risk of bias and imprecision and the results were mixed. In the analysis that included the largest number of studies (n=350 participants), there was a benefit on acute distress: SMD -0.35 (95% CI -0.57, -0.13). There were no data for other critical outcomes (pain, fear) due to the inability of included children to provide self-report as a result of their young age.

Implementation considerations:

Education of parents about pain management during childhood vaccination is highly valued by the panel and this recommendation applies to parents of children aged 0-17 years. While studies only included parents of young children, this intervention is expected to have benefit across childhood as parents are expected to use their knowledge to teach their children about this topic, advocate for better care for their children across different health care settings, and use interventions they are educated about to help make vaccinations more comfortable for their children, regardless of age. Learning to make vaccine injections more comfortable for their children can improve parent self-efficacy. Children are also expected to benefit as they may be participants in the learning.

All of the educational delivery methods employed in included studies (verbal instruction, pamphlets, videos) and venues (hospital, clinic) are currently used to educate the public about immunization and are options for providing education about vaccination pain management. Additional resources (supplies, personnel) may be required to educate and support parents to be able to implement pain interventions. These resources are considered justified to mitigate iatrogenic harm from needle-induced pain. Currently, evidence-based resources have been incorporated into the Immunize Canada website (www.immunize.ca) and a national immunization *app* (http://immunize.ca/en/app.aspx)[22] distributed to the public by Immunize Canada at no cost. There are also numerous videos posted on the internet as well; however, their effectiveness in increasing utilization of interventions for pain management has not been established. Of note, parents who are particularly distressed themselves may not be able to successfully lead some interventions (e.g., distraction) and may require additional training or support.

48. Should parents be educated about vaccine injection pain management on the day of vaccination?

We recommend education of parents about pain management on the day of vaccination (strong recommendation, very low confidence in estimates of effect).

Four studies evaluated education of parents of children up to 6 years of age on the day of vaccination[24,239,249,281]. In included studies, parents were trained in clinics using a variety of techniques, including: verbal instruction, pamphlets, computer or videos. There was low to very low quality of evidence due to risk of bias and imprecision for one of the critical outcomes (use of pain interventions)

and results were mixed for this outcome. In the analysis including the largest number of participants (n=239), there was a benefit for parent use of intervention: RR 2.42 (95% CI 1.47, 3.99) (N.B. better indicated by higher number). There was a benefit for child use of intervention in one study including 60 children[249]: SMD 1.93 (95% CI 1.31, 2.55). There was no evidence of a benefit for pain and results were mixed for measures of child distress. In the analysis including the largest number of children (n=422), there was no evidence of a benefit for acute distress: SMD 0.05 (95% CI -0.89, 0.99). There was no data for the other critical outcome (fear).

Implementation considerations:

Education of parents about pain management during childhood vaccination is highly valued by the panel and this recommendation applies to parents of children 0-17 years. While the literature base primarily consists of parents with young children, this intervention is expected to have benefit across childhood as parents will teach, advocate for, and use the education to help their children, regardless of age.

Additional resources (supplies, personnel) may be required to educate and support parents to be able to implement pain interventions. All of the educational delivery methods employed in included studies (verbal instruction, pamphlets, videos) are currently used to educate the public about immunization in general in clinical settings where vaccine injections are undertaken. These resources are considered justified to mitigate iatrogenic harm from needle-induced pain and fear. Evidence-based resources are currently available from Immunize Canada (www.immunize.ca), including; pamphlets, videos, and a national immunization *app* distributed at no cost (http://immunize.ca/en/app.aspx)[22]

Depending on the timeline for use of specific interventions, they may or may not be feasible on the day of education (e.g., topical anesthetics); education is therefore also recommended ahead of time (see recommendation #47). Prior education may have the additional benefits of: 1) reducing parental (and child) anxiety on the day of vaccination because parents (and children) are knowledgeable about how to comfort children and aware that children's comfort level during the procedure is being addressed by immunizers; 2) improving parent (and child) competency in implementing pain and fear management interventions because they have had time to learn about different interventions (including opportunities to have their questions answered) and possibly practice ahead of time. It may also reduce the potential for disappointment from not being able to optimally implement pain treatments (e.g., inaccurate application of topical anesthetics) or inability to access specific options that require planning and/or preparation (e.g., topical anesthetics, sweet-tasting solutions).

Of note, additional data for the effects of parent education can be extracted from clinical questions for individual interventions whereby parents were instructed and involved in administering the intervention. Parents who are particularly distressed themselves may not be able to successfully lead some interventions (e.g., distraction) and may require additional training or support.

Education of individuals undergoing vaccinations

The provision of information about upcoming stressful medical procedures to individuals undergoing them is believed to assist with expectations about the procedure and coping responses[282]. The optimal content and timing of information provision is unknown. It is generally accepted that information about what will happen (procedural information), how it will feel (sensory information) and how to cope (training in strategies to mitigate pain and fear) should be included[283,284]. The information provided should be consistent with the individual's developmental level, health literacy and be culturally sensitive. Information provision methods include: face-to-face, written, or video instruction. In terms of timing, the need for the individual to be able to use the information and prepare must be balanced with avoiding the creation of undue anticipatory anxiety. Several days ahead of time appears to be appropriate for older children undergoing more involved procedures[283]. There may be

differences in the information needs of individuals according to factors such as invasiveness of the procedure, previous experience, cognitive development, and coping style that require consideration.

It has been recommended that the majority of information provision be carried out ahead of time and that focus be given to coping strategies at the time of the procedure. Providing detailed sensory information at the time of the procedure may overwhelm individuals and increase distress[282,283] (e.g., see also recommendation #29).

The panel reviewed the specific evidence for the effectiveness of educating individuals about pain and fear management on the day of vaccination (recommendation #49). Education *prior* to vaccination day was not included in the evidence base and regarded as a good clinical practice by the panel[282,284].

49. Should children >3 years and adults be educated about vaccine injection pain management on the day of vaccination?

We recommend education of children >3 years and adults about pain management on the day of vaccination (strong recommendation, very low confidence in estimates of effect).

One study involving 51 female children undergoing vaccination aged 11 to 12 years in a school setting was included in the systematic review[285]. Children in the intervention groups were provided with 10 minutes of detailed information about the infectious disease being vaccinated against, the vaccination procedure and cognitive coping techniques. Then they either practiced by imagining the vaccine injection or asked questions. There was very low quality of evidence for the critical outcome of fear due to risk of bias and imprecision. The effects were mixed; there was a benefit for pre-procedural fear [SMD -0.67, 95% CI -1.28, -0.07)] but not acute fear [SMD -0.63 (95% CI -1.62, 0.36)]. There was no data for the critical outcome of pain. In the included study, children were vaccinated in groups of 5 and there may have been some contamination between educated and non-educated groups.

<u>Implementation considerations</u>:

The panel strongly recommended the education of children >3 years and adults on the day of vaccination despite the lack of evidence for a benefit on pain because: 1) we place a high value on educating individuals about pain management during vaccination and providing them with coping strategies that they can use to improve their experience during vaccination as well as other stressful procedures; 2) it demonstrates a patient-centred approach; and 3) it can improve satisfaction with the vaccination experience and interactions with health care providers; 4) it can improve acceptability of vaccinations; and 5) individuals are better empowered to direct aspects of their health care.

Additional resources are required to provide developmentally appropriate education and support of individuals so that they are able to implement interventions. These resources are considered justified to mitigate iatrogenic harm from needle-induced pain and to improve self-efficacy with the interventions. Education on the day of vaccination should focus on coping strategies with demonstrated benefit (vs. a detailed sensory explanation of the impending pain[282]. Specifically, individuals can be taught about the age-matched recommended strategies in this guideline, such as sitting up (recommendation #11), topical anesthetics (recommendation #17 and #18), and distraction for children >3-12 years (see recommendations #35, #36, #37, #41). Importantly, opportunities to learn about pain management can and should also occur ahead of time[286], which also maximizes the possibility that interventions of choice can be used on the day of vaccination (see also recommendation #47).

Additional data for the effects of education of individuals can be extracted from clinical questions for individual treatments whereby individuals were instructed and involved in administering the intervention. Future research should be conducted on the optimal timing and content of education for individuals of various ages, coping styles, and levels of experience.

Additional Tools for Guideline Implementation

How should recommendations be implemented for individuals?

Some judgement is required regarding the selection of interventions to use to manage vaccination pain as they are not all necessarily appropriate, helpful and/or needed in every situation. No single intervention is expected to prevent pain (i.e., achieve a level of pain of "0"). Individual interventions can be combined, as appropriate, in order to improve the effects. For young and school-age children, a more comprehensive approach is recommended due to the high levels of child distress associated with vaccine injections, child focus on needle pain (patient-important outcome), and potential for long-term harm of unmitigated pain, including the development of needle fears and health care avoidance behaviours. As children mature and are able to give their preferences, a more self-directed and individualized approach can be used.

Who should adopt these guidelines?

Organizations overseeing immunization and health care providers who administer vaccines are encouraged to adopt these recommendations for implementation in their settings. Furthermore, these organizations and health care providers are asked to incorporate teaching of clinicians, parents and individuals undergoing vaccine injections about the recommendations according to their usual methods (e.g., pamphlets, videos and/or one-on-one teaching). Importantly, the WHO has indicated that mitigating pain at time of vaccination should be considered part of good immunization and clinical practice and has promoted interventions included in this guideline for national programmes[35].

Parents of children undergoing vaccine injections and individuals undergoing vaccine injections themselves should be given information about pain interventions directly as well. Some potential settings and opportunities for education include: hospital-based prenatal classes, postpartum hospital ward, outpatient clinics, public health departments and home visits, pharmacy-based vaccination clinics, school-based vaccination clinics, occupational health clinics, and extracurricular-based education programs.

Where can our resources be located?

Currently, our resources have been incorporated into the Immunize Canada website (www.immunize.ca) and an immunization *app* distributed to the public by Immunize Canada free of charge to the public (http://immunize.ca/en/app.aspx)[22]. They are also available on the HELPinKids&Adults website: http://phm.utoronto.ca/helpinkids.

What about the cost of implementing these guidelines?

As described above, there is general agreement that minimizing discomfort during vaccinations is a part of good immunization and clinical practice (i.e., pain management is included in the process of vaccination) and hence, it is the responsibility of the immunizer. However, there has not been a national or international strategy to educate clinicians about best practices and/or to provide them with the necessary support to be able to do so. It is therefore recommended that agencies administering vaccine injections review their current policies for vaccine administration and ensure that: 1) adequate education about pain management is included for health providers and the public and, 2) that resources are provided at the point of care in order to be able to mitigate vaccine-injection associated pain.

After the cost of education, many of the interventions included in this guideline are cost-neutral. Some of the interventions, however, will incur ongoing costs (e.g., topical anesthetics, sweet-tasting solutions). Removal of practices currently in widespread use that incur costs but are not evidence-based (e.g., disinfection of skin with alcohol)[287] can offset some of the additional expenses associated with providing pain mitigation interventions. Individuals undergoing vaccination can be asked to pay for interventions and these interventions can then be made available in the vaccination setting on the day of

vaccination to improve convenience and feasibility of their use. However, some individuals may be unwilling to pay for interventions. This should not be interpreted as ambivalence about pain; specifically, some individuals may be unwilling to pay simply because they hold the belief that the cost of pain treatment is the responsibility of those providing the vaccines[6]. Individuals may also have limited financial means to cover the associated costs of particular interventions despite a desire to use them.

The costs to manage pain during vaccination must also consider the costs of long-term harm from unmitigated pain, including the negative impact on health outcomes due to non-compliance with immunization and other health care interventions, and the costs for the treatment of needle fears that have developed due to poorly managed pain.

Pharmaceutical companies involved in the manufacture and sale of vaccines are encouraged to develop vaccines that are less painful and that can be delivered in less painful ways. Analgesic manufacturers should consider adding interventions with vaccine shipments.

Measuring pain, fear, and distress in the vaccination context

Guidance is offered regarding assessment of the relevant constructs associated with the recommendations included in the guideline (i.e., pain, fear, distress) (**Appendix**). This is needed because the ability to determine the suitability of interventions and/or to judge their effectiveness is based on the ability to assess the relevant constructs accurately and reliably.

In the previous guideline, we provided guidance regarding the assessment of pain and distress across childhood[20], and this remains similar in version 2.0. Self-report tools are recommended for use with children 3 years of age and above[288]. However, it should be noted that in young children (< 7 years), self-report may not be reliable[44,45]; thus, we recommend multiple informants be asked for this information (e.g., child, caregiver, health care provider). Expanding on the guidance to include adults, the same method of pain assessment recommended for children aged 8 years and above is recommended for use in adults: specifically, a 0-10 Numerical Rating Scale (NRS)[289]; whereby 0 means no pain and 10 is the worst pain possible. If any visual or auditory impairment are present, these should be addressed (e.g., adapting written materials, ensuring the patient can see you while you speak[290]. Even in populations with reduced communication skills such as older individuals with mild to moderate dementia, self-report may be possible (e.g., yes/no, pointing to a response on a scale)[291].

For populations with more significant cognitive impairments who are nonverbal, consideration of behavioural indicators of pain has been recommended[292-295]. The Checklist of Nonverbal Pain Indicators (CNPI)[296] has been supported for procedural pain assessment in adult populations who are nonverbal and/or cognitively impaired[295,297,298] while the revised FLACC (r-FLACC)[299,300] is clinically feasible and appropriate for clinicians to use with children[301]; note that caregivers may be asked to provide individualized behaviours as part of the tool. Parents can use the Non-Communicating Children's Pain Checklist – Postoperative Version[293] [note that due to length this is not included in the **Appendix** but this tool is freely available at: pediatric-pain.ca/our-measures]. In the context of vaccine injections, observable behaviours are not specific to pain and may indicate another source of arousal (e.g., fear)[291]. They are therefore best conceptualized as indicators of distress. Caregivers who are knowledgeable of the typical pain and distress behaviours displayed by the individual who is nonverbal can be a helpful source of information.

With respect to the assessment of fear specifically in children able to provide self-report (5-12 years), either the Children's Fear Scale (faces fear scale)[302] or Verbal Descriptor Scale (i.e., before the needle: *How scared of getting the needle are you: not at all, a little bit, a medium amount, a lot, or very much/most possible?*; after the needle: *How scared where you during the needle: not at all; a little bit; a medium amount; a lot; or very, very much/most possible?*) is recommended. Children 8 years and above and adults can use a 0-10 NRS (e.g., where 0=no fear/not scared at all and 10=most fear/most

scared possible). We recommend the Faces Anxiety Scale[303,304] for adults with physical impairment or otherwise compromised health.

Screening of individuals with high levels of needle fear

Individuals with high levels of needle fear should be identified before vaccine injections as they can benefit from interventions designed to treat needle fear (and the use of traditional pain management interventions during vaccinations will likely be ineffective for these individuals). It should be noted, however, that individuals with extreme fear levels may simply avoid presenting for vaccinations at all. Forcing an individual with a high degree of fear to undergo a vaccination will likely result in a more distressing and painful experience and escalate the fear the next time. If an individual is forcibly restrained in order to accomplish the procedure, not only is that more unpleasant for the individual and onlookers, the individual (and his/her caregivers, if applicable) will have highly negative expectations of future procedures likely leading to avoidance.

A high level of needle fear is defined as occurring when an individual shows persistent, intense anxiety or fear in anticipation of or in response to a needle procedure. Individuals who are so highly fearful of needles they are considered "phobic" will try to avoid or escape any situation in which a needle is given (e.g., run out of the room, flail) or else the needle procedure is endured with intense distress (e.g., freeze, have a temper tantrum, cry, scream, tremble). The role of the immunizer in this context is to screen for the presence of a high level of needle fear (not to diagnose a phobia); the recommended screening process is described next.

Individuals for whom vaccination is being recommended or considered can be asked about fear of needles. Examples of questions for older children (>10 years) and adults include: *How afraid of needles are you – not afraid, a little bit, medium/moderate amount, a lot, or the most afraid possible? Do you think this is higher than it should be? Do you avoid getting needles because you are afraid?* Parents of children can be asked analogous questions. Younger children (5-10 years) can be asked: *How scared of needles are you - not at all scared; a little bit; medium amount; a lot; very, very much/ most possible? Do you try really hard to miss getting the needle because you are so scared?* If individuals respond to these questions in a way that suggests they have a high level of fear (with or without avoidance), then clinicians should strongly consider postponing the procedure until the fear has been adequately treated. We recommend that the actual treatment of the fear is completed by individuals with mental health expertise following the recommendations outlined in the companion guideline[34]; thus, the role of the immunizers is to recommend that the individual seek treatment for the needle fear prior to being vaccinated. Potential referral sources include anxiety clinics located in health care centres as well as licensed practitioners of psychology and psychiatry with expertise in the treatment of anxiety disorders (e.g., the website of the College of Psychologists of Ontario contains a public register of members which is searchable by geographic location and/or areas of practice; an analogous register of psychiatrists is available on the College of Physicians and Surgeons of Ontario website). Vaccination need not be delayed substantially for as little as one session of several hours may be required to successfully treat high levels of needle fear[34].

Screening of individuals with a history of fainting

Fainting can occur in individuals with or without needle fear; that is, not everyone who is at risk for fainting during vaccination has a high level of needle fear. Therefore, people undergoing vaccination (and/or parents of younger children if present) should be asked about prior experiences with fainting to determine if intervention is required as the risk of experiencing future episodes increases with a history of fainting[125,305]. Examples of questions that could be asked to identify history of fainting include: *Have you ever felt quite dizzy, light headed, nauseated* (for children: *like you are going to throw up*), *and/or sweaty when having a needle procedure before?* [This question targets prodromal symptoms, which, if they occur, can be warning flags that fainting is imminent. However, not everyone experiences a

prodromal period]. *Have you ever fainted, that is, lost consciousness, or passed out, during a needle procedure?* If the answer is yes to either of these questions, interventions should be considered for preventing fainting.

Documentation tool

In our original guideline[20], we developed a documentation checklist for clinicians that could be used to keep track of pain interventions and their effects. This tool has been updated and expanded to incorporate the new recommendations (**Appendix**). This tool can be used for clinical and research purposes to track intervention use and effectiveness. It can be customized to meet the needs of users in different settings. The immunization *app* users may also be able to self-report pain for each type of vaccine they receive in the *app* (this is planned for future applications of the *app*).

Limitations of the guideline

Version 2.0 of the HELPinKids&Adults clinical practice guideline takes a broad approach to addressing vaccination pain by including individuals spanning all developmental stages (infancy through adulthood) and including relevant outcomes for specific interventions. The recommendations are limited to the available evidence at the time the systematic reviews were undertaken. Across clinical questions, there was a small number of included studies (and participants) and methodological limitations that impacted on the confidence in the estimates of effect of different interventions. In several instances, we used indirect evidence (i.e., outside of the context of vaccine injections, for example, venipuncture) to base our decisions. The evidence base for interventions was not equally available for all age groups and some extrapolation of findings was made across developmental periods based on clinical judgement, related literature and panel consensus. From adolescence through adulthood, there was very little research, precluding examination of interventions in different age groups (e.g., young adult vs. elderly) and health status (e.g., healthy vs. compromised). The guideline does not provide specific guidance for individuals with co-morbidities (e.g., cancer, depression, autism); however, these individuals were not specifically excluded from the evidence base and may have been included in the evidence for certain clinical questions. There was a dearth of literature for many important outcomes (e.g., vaccine compliance).

The guideline excluded interventions which cannot be implemented by immunizers because of regionally approved labelling instructions or availability of specific products (e.g., varying the route of administration of a vaccine or choosing among vaccines to reduce pain). In addition, clinical questions regarding the impact of pre-emptive analgesia and interventions aimed at reframing memory of past vaccination experiences were excluded because the data was scant, of poor quality, and mostly included indirect evidence whereby the populations/context were deemed to be too different for extrapolation to vaccination. While excluded, the questions are deemed highly clinically relevant and are highlighted in the section titled "**Future Research**". These and other issues are further explored in a separate paper by Noel et al. (2015)[306].

Setting and situational factors (mass and school based programs)

The guideline does not include recommendations for setting and situational factor interventions to reduce pain due to lack of experimental work in this area. Based on a qualitative review of available literature[153,307-310], we offer some good clinical practice recommendations for vaccination programs involving mass vaccinations, particularly school-based vaccination programs, with the goal of further reducing pain and fear. While there is no consensus on whether individuals should be vaccinated with a (helpful) peer present or not, there does appear to be general agreement that individuals should not be visible to groups of others waiting to receive vaccinations. Given that the potential harm of negative vicarious learning seems to outweigh potential benefit of appropriate modeling, privacy is

recommended. This could be achieved by using separate rooms or with privacy screens (although privacy screens do not block sound). There is general consensus that large groups of individuals should not be kept waiting within the vaccination area or lined up just outside. If groups of individuals are waiting together, it can increase fear within individuals and risk emotion contagion (which can increase pain sensation). Overall, the environment should be kept as calm and non-threatening as possible (e.g., keep distress-provoking objects such as needles and syringes out of sight).

Future Research

In the process of generating clinical questions and synthesizing this literature, many areas for future research were identified. Data are needed on the painfulness of different vaccines (including their route of administration), aspects of vaccine injection technique (e.g., speed of injection, injection in a single limb for multiple vaccine injections) and vaccine formulations and delivery systems that minimize pain. Given the influential role of memory for pain and fear in subsequent pain experience [311,312], research is recommended that specifically examines the efficacy of memory reframing interventions on subsequent outcomes (e.g., pain, fear). Likewise, studying the impact of past pain interventions (pre-emptive analgesia) on subsequent pain during future procedures and vaccine compliance is important in order to document the long term impact of interventions for pain. More research is recommended across the lifespan, including the elderly with and without impaired cognition to allow developmental stage/age-based specificity in recommendations. School-based vaccinations should be specifically targeted for research due to the large number of school aged children immunized each year in Canada and the unique issues and challenges related to this context in order to facilitate more positive experiences. Outcomes of studies should also extend beyond pain intensity to reflect the impact of interventions on other important outcomes identified by the broader community of stakeholders involved in vaccination (e.g., vaccination compliance).

Updates

An update of this guideline is planned for the next 5-10 years (i.e., 2019-2024) according to the availability of new evidence, input by stakeholder groups and project funding.

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A Taddio declares a grant from Pfizer, and study supplies from Natus and Ferndale.
CT Chambers declares consultation fees from Abbvie.
E Lang is a member of the GRADE working group and declares consultation fees from the International Liaison Committee on Resuscitation (ILCOR).
L Bucci declares a relationship with government agencies and grants from Merck, GSK, Novartis, Sanofi, and Pfizer.
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APPENDIX

Table 1. Recommendations for reducing pain (and associated outcomes) during vaccination

Treatment	**Recommendation**	**Confidence**	**Infant & young child** (≤ 3 yr)	**Child** (3-12 yr)	**Adolescent** (12-17 yr)	**Adult** (≥ 18 yr)
Strong Recommendations						
Procedural Interventions						
No aspiration	We recommend no aspiration during intramuscular vaccine injections	Very low	✓	✓	✓	✓
Order of injection	We recommend injecting the most painful vaccine last during vaccine injections	Moderate	✓	✓	✓	✓
Physical Interventions						
Breastfeeding*	We recommend breastfeeding	Very low	✓	-	-	-

	during vaccine injections		(0-2 yr)			
Positioning - Skin-to-skin contact**	We recommend skin-to-skin contact during vaccine injections	Moderate	✓ (0-1 mo)	-	-	-
Positioning - Holding**	We recommend holding during vaccine injections	Very low	✓	-	-	-
	If holding is not used during vaccine injections, we recommend a combined holding intervention (including patting and/or rocking) after vaccine injections	Low	✓	-	-	-
Positioning - Sitting up	We recommend sitting up during vaccine injections	Low	-	✓	✓	✓
Pharmacological Interventions						
Topical anaesthetics	We recommend topical anesthetics before vaccine injections	Very low	✓	✓	[a]	[a]
Sweet-tasting	We recommend sucrose solutions	Moderate	✓	-	-	-

solutions**/***	before vaccine injections		(0-2 yr)			
	We recommend glucose solutions before vaccine injections	Moderate	✓ (0-2 yr)	-	-	-
Process Interventions						
Education of clinicians	We recommend education of clinicians administering vaccine injections about vaccine injection pain management	Low	✓	✓	✓	✓
Parent presence	We recommend presence of parents during vaccine injections	Very low	✓	✓ (≤ 10 yr)	-	-
Education of parents	We recommend education of parents about pain management for vaccine injection before the day of vaccination	Low	✓	✓	✓	-
	We recommend education of parents about pain management for	Very low	✓	✓	✓	-

	vaccine injection on the day of vaccination					
Education of individuals undergoing vaccination	We recommend education of individuals about pain management for vaccine injection on the day of vaccination	Very low	-	✓	✓	✓
Weak Recommendations						
Procedural Interventions						
Simultaneous injection	We suggest simultaneous injections (rather than sequential injections) during vaccine injections	Low	✓ (0-1 yr)[a] See below	[a]	-	-
	We suggest ***against*** simultaneous injections during vaccine injections	Very low	✓ (>1-3 yr)[a]	✓ (≤ 10 yr)	-	-
Vastus Lateralis	We suggest the vastus lateralis (rather than the deltoid) as the site	Low	✓ (0-11 mo)	-	-	-

	of injection during vaccine injections					
Physical Interventions						
Breastfeeding*	If breastfeeding is not used during vaccine injections, we suggest breastfeeding before vaccine injections	Low	✓ (0-2 yr)	-	-	-
Non-nutritive sucking**	We suggest non-nutritive sucking (using a thumb/finger, pacifier) during vaccine injections	Low	✓ (0-2 yr)	-	-	-
Vibrating device with cold	We suggest an external vibrating device with cold during vaccine injections	Low	-	✓	✓	-
Muscle tension	We suggest muscle tension for vaccine injections in individuals with a history of fainting	Very low	-	✓ (≥ 7 yr)	✓	✓

Manual tactile stimulation	We suggest ***against*** manual tactile stimulation during vaccine injections	Very low	✓	✓	✓	✓
Warming the vaccine	We suggest ***against*** warming the vaccine before vaccine injections	Low	✓	✓	✓	✓
Pharmacological Interventions						
Topical anaesthetics	We suggest topical anesthetics before vaccine injections	Moderate	[a]	[a]	✓	✓
Topical anaesthetics & breastfeeding*	We suggest combining topical anesthetics before vaccine injections and breastfeeding during vaccine injections	Low	✓ (0-2 yr)	-	-	-
Sweet-tasting solutions & non-nutritive sucking**/***	We suggest sweet-tasting solutions (sucrose, glucose) before vaccine injections and non-nutritive sucking (thumb/finger, pacifier) during vaccine injections	Very low	✓ (0-2 yr)	-	-	-

Vapocoolants	We suggest ***against*** applying vapocoolants before vaccine injections	Low	✓	✓	✓	[a]
	We suggest that vapocoolant spray be used before vaccine injections	Low	[a]	[a]	[a]	✓
Acetaminophen	We suggest ***against*** giving acetaminophen before vaccine injections	Low	✓	✓	✓	✓
Ibuprofen	We suggest ***against*** giving ibuprofen before vaccine injections	Very low	✓	✓	✓	✓
Sweet-tasting solutions & breastfeeding	We suggest ***against*** using sweet-tasting solutions (sucrose, glucose) and breastfeeding in combination before vaccine injections	Low	✓ (0-2 yr)	-	-	-
Psychological Interventions						
Verbal signal of impending	We suggest a verbal signal of the impending procedure (vs. a signal	Very low	✓	✓	✓	✓

procedure	of impending pain) before vaccine injections					
Distraction	We suggest directed video distraction during vaccine injections	Very low	✓	[a]	-	-
	We suggest directed toy distraction during vaccine injections	Very low	✓	-	-	-
	We suggest non-directed toy distraction during vaccine injections	Very low	✓	-	-	-
	We suggest verbal distraction during vaccine injections	Low	-	✓	-	-
	We suggest video distraction during vaccine injections	Very low	[a]	✓	-	-
	We suggest music distraction during vaccine injections	Low	-	✓	[a]	[a]
	We suggest ***against*** music	Very low	-	[a]	✓	✓

	distraction during vaccine injections					
	We suggest ***against*** visual distraction during vaccine injections	Very low	-	-	-	✓
Breathing distraction	We suggest breathing with a toy distraction (e.g., blowing bubbles, pinwheel) during vaccine injections	Very low	-	✓	-	-
	We suggest ***against*** breathing without a toy distraction (blowing, deep breathing) during vaccine injections	Very low	-	✓	-	-
	We suggest ***against*** breathing interventions (cough) during vaccine injections	Low	-	✓	✓	[a]
	We suggest breathing interventions (cough, breath-hold) during vaccine	Very low	-	[a]	[a]	✓

	injections					
Using suggestion	We suggest ***against*** using false suggestion during vaccine injections	Low	✓	✓	✓	✓
Using reassurance	We suggest ***against*** using repeated reassurance during vaccine injections	Very low	✓	✓	✓	✓

[a] see elsewhere in the table for a recommendation in this age group.

* alternatively, bottle feeding with expressed breastmilk or formula can be used or combined interventions which simulate breastfeeding (holding, sweet-tasting solution, sucking), as appropriate.

** if not breastfeeding.

*** alternatively, if oral rotavirus vaccine is being administered at the same time as injectable vaccines, rotavirus vaccine can be given first as it contains sucrose.

Abbreviations: yr = year; mo = month

Recommendations for Reducing Vaccination Pain in Children 0-3 years

Ahead of time → **At vaccination visit** → **During vaccination**

Procedural Strategies

- No aspiration
- Most painful last
  AND/OR
  - Simultaneous injection (0-1 yr)
- Vastus lateralis (0-11 months)

Physical Strategies

- Breastfeeding before, during and after injection (0-2 yr)*

OR

- Positioning - skin to skin (0-1 month) or holding (0-3 yr) before, during and after injection
- Sweet-tasting solution – sucrose or glucose before injection (0-2 yr)**
- Sucking/pacifier before, during and after injection (0-2 yr)

Psychological Strategies

- Distraction: toy, video
- Interaction/Wording:
  DO: use neutral words to signal the impending procedure
  DON'T: use repeated reassurance, suggest it will not hurt

Pharmacological Strategies

- Topical anesthetics:
  liposomal lidocaine, amethocaine, or lidocaine-prilocaine 20-60 minutes before injection***

Process Strategies

- Education about pain management for providers and caregivers
- Caregiver presence

* Alternatives include bottle feeding
** Alternatives include oral rotavirus vaccine (in infants scheduled to receive it at the same time as injectable vaccines)
*** Check product monograph

HELP Eliminate Pain in Kids & Adults

Recommendations for Reducing Vaccination Pain in Children 3-12 years

Ahead of time → **At vaccination visit** → **During vaccination**

Procedural Strategies

- No aspiration
- Most painful last

Physical Strategies

- Positioning – sitting upright
- External vibrating device with cold
- Muscle tension (≥ 7 yrs, if history of fainting)

Psychological Strategies

- Distraction:
  music , video , verbal , breathing with a toy
  (e.g., blowing bubbles, pinwheel)
- Interaction/Wording:
  DO: use neutral words to signal the impending procedure
  DON'T: use repeated reassurance, suggest it will not hurt

Pharmacological Strategies

- Topical anesthetics:
  liposomal lidocaine,
  amethocaine, or lidocaine-
  prilocaine 20-60 minutes before
  injection*

Process Strategies

- Education about pain management for providers, caregivers and children
- Caregiver presence (0-10 years)

Strategies for High Needle Fear

- Exposure-based therapy
  (≥ 7 yrs)
- Applied tension (≥ 7 yrs,
  if history of fainting)

* Check product monograph

HELP Eliminate Pain in Kids & Adults

Recommendations for Reducing Vaccination Pain in Adolescents 12-17 years

Ahead of time → **At vaccination visit** → **During vaccination**

Procedural Strategies

- No aspiration
- Most painful last

Physical Strategies

- Positioning – sitting upright
- External vibrating device with cold
- Muscle tension (if history of fainting)

Psychological Strategies

- Interaction/Wording:
  DO: use neutral words to signal the impending procedure
  DON'T: use repeated reassurance, suggest it will not hurt

Pharmacological Strategies

- Topical anesthetics:
  liposomal lidocaine, amethocaine, or lidocaine-prilocaine 20-60 minutes before injection*

Process Strategies

- Education about pain management for providers, caregivers and individuals

Strategies for High Needle Fear

- Exposure-based therapy
- Applied tension (if history of fainting)

* Check product monograph

HELP Eliminate Pain in Kids & Adults

Recommendations for Reducing Vaccination Pain in Adults

Ahead of time → **At vaccination visit** → **During vaccination**

Procedural Strategies

- No aspiration
- Most painful last

Physical Strategies

- Positioning – sitting upright
- Muscle tension (if history of fainting)

Psychological Strategies

- Breathing interventions (cough, breath-hold)
- Interaction/Wording:
  DO: use neutral words to signal the impending procedure
  DON'T: use repeated reassurance, suggest it will not hurt

Pharmacological Strategies

- Topical anesthetics:
  liposomal lidocaine, amethocaine, or lidocaine-prilocaine 20-60 minutes before injection*
- Vapocoolant right before injection

Process Strategies

- Education about pain management for providers and individuals

Strategies for High Needle Fear

- Exposure-based therapy
- Applied tension (if history of fainting)

* Check product monograph

HELP Eliminate Pain in Kids & Adults

Health Care Provider Pain, Distress and Fear Assessment Tools

HEALTH CARE PROVIDER-RATED DISTRESS

Modified Behavioural Pain Scale (MBPS) For Children ≤ 18 Months

FACIAL EXPRESSION

Definite positive expression: smiling	☐ 0
Neutral expression	☐ 1
Slightly negative expression: for example, grimace	☐ 2
Define negative expression: that is, furrowed brows, eyes closed tightly	☐ 3

CRY

Laughing or giggling	☐ 0
Not crying	☐ 1
Moaning, quietly vocalizing, gentle or whimpering cry	☐ 2
Full lunged cry or sobbing	☐ 3
Full lunged cry, more than baseline cry: to be scored only if infant crying at baseline	☐ 4

MOVEMENTS

Usual movements/activity, or resting/relaxed	☐ 0
Partial movement or attempt to avoid pain by withdrawing the limb where puncture is done	☐ 2
Agitation with complex movements involving the head, torso or the other limbs, or rigidity	☐ 3

TOTAL SCORE (0-10) _____

Reprinted from Journal of Pain and Symptom Management, 10, Taddio A, Nulman I, Koren BS, Stevens, B, Koren, G. A revised measure of acute pain in infants, 456-463, Copyright 1995, with permission from Elsevier.

Face Legs Activity Cry Consolability (FLACC) For Children >18 Months

Categories	Scoring 0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractible	Difficulty to console or comfort

TOTAL SCORE (0-10) _____

Revised-FLACC For Children With Cognitive Impairment

Category	Scoring 0	1	2
Face Individualized behaviour: _____	- No particular expression or smile	- Occasional grimace/frown; withdrawn or disinterested; appears sad or worried	- Consistent grimace or frown; frequent/constant quivering chin, clenched jaw; distressed-looking face; expression of fright or panic
Legs Individualized behaviour: _____	- Normal position or relaxed; usual tone & motion to limbs	- Uneasy, restless, tense; occasional tremors	- Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking
Activity Individualized behaviour: _____	- Lying quietly, normal position, moves easily; regular, rhythmic respirations	- Squirming, shifting back and forth, tense or guarded movements; mildly agitated (e.g., head back & forth, aggression); shallow, splinting respirations, intermittent sighs	- Arched, rigid or jerking; severe agitation; head banging; shivering (not rigors); breath holding, gasping or sharp intake of breaths, severe splinting
Cry Individualized behaviour: _____	- No cry/verbalization	- Moans or whimpers; occasional complaint; occasional verbal outburst or grunt	- Crying steadily, screams or sobs, frequent complaints; repeated outbursts, constant grunting
Consolability Individualized behaviour: _____	- Content & relaxed	- Reassured by occasional touching, hugging or being talked to. Distractible.	- Difficult to console or comfort; pushing away caregiver, resisting care or comfort measures

TOTAL SCORE (0-10) _____

Checklist of Nonverbal Pain Indicators for Adults with Cognitive Impairment

Behavior (all scored 0 = not present; 1 = observed)
1) Vocal complaints: nonverbal (sighs, gasps, moans, groans, cries)
2) Facial grimaces/winces (furrowed brow, narrowed eyes, clenched teeth, tightened lips, jaw drop, distorted expressions)
3) Bracing (clutching or holding onto furniture equipment, or affected area during movement)
4) Restlessness (constant or intermittent shifting of position, rocking, intermittent or constant hand motions, inability to keep still)
5) Rubbing (massaging affected area)
6) Vocal complaints: verbal (words expressing discomfort or pain [e.g., "ouch", "that hurts"]; cursing during movement; exclamation of protest [e.g., "stop," "that's enough"])

TOTAL SCORE (0-6) _____

CNPI figure has been reproduced from https://www.healthcare.uiowa.edu/igec/tools/pain/nonverbalPain.pdf
Feldt KS. The checklist of nonverbal pain indicators (CNPI). Pain Management Nursing 2000;1:13-21 .

r-FLACC figure has been reproduced from Pediatric Anesthesia, 16, Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment, 258-265, Copyright 2006, with permission from Wiley.

PARENT-RATED DISTRESS (Children ≤ 3 Years; Should Be Used in Combination with Self-Report in Children 3-7 years)*

Numerical Rating Scale (NRS)

"Tell me how much distress you think your child had from the vaccine injection from 0 to 10, where 0 is no distress and 10 is the worst distress possible."

Visual Analog Scale (VAS)

No distress — Worst distress possible

INDIVIDUAL SELF-REPORTED PAIN AND FEAR

Pieces of Hurt Tool for Children 3-6 Years*

1. Say to the child: *"I want to talk to you about the hurt you may be having right now."*
2. Align the pieces of hurt (e.g., poker chips) horizontally in front of the child on the bedside table, a clipboard, or other firm surface.
3. Tell the child, *"These are pieces of hurt."* Beginning at the chip nearest the child's left side and ending at the one nearest the right side, point to the chips and say, *"This (first chip) is a little bit of hurt and this (fourth chip) is the most hurt you could ever have."* For a young child or for any child who may not fully comprehend the instructions, clarify by saying, *"That means this (one) is just a little hurt, this (two) is a little more hurt, this (three) is more yet, and this (four) is the most hurt you could ever have."*
   - Do not give children an option for zero hurt. Research with the Pieces of Hurt Tool has verified that children without pain will so indicate by responses such as, *"I don't have any."*
4. Ask the child, *"How many pieces of hurt do you have right now?"*
   - After initial use of the Pieces of Hurt Tool, some children internalize the concept "pieces of hurt". If a child gives a response such as "I have one right now", before you ask or before you lay out the chips, proceed with instruction #5.
5. Record the number of chips on the Pain Flow Sheet.
6. Clarify the child's answer by words such as, *"Oh, you have a little hurt? Tell me about the hurt."*

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Faces Pain Scale - Revised (FPS-R) for Children ≥ 5 Years*

In the following instructions, say "hurt" or "pain," whichever seems right for a particular chid.
These faces show how much something can hurt. This face [*point to left-most face]* shows no pain. The faces show more and more pain *[pain to each from left to right]* up to this one *[point to right-most face]* – it shows very much pain. Point to the face that shows how much you hurt *[right now].*
Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'very much pain.' Do not use words like 'happy' and 'sad'. This scale is it intended to measure how children feel inside, not how their face looks. www.iasppain.org/fpsr

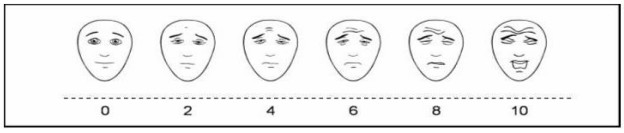

Figure reproduced with permission of the International Association for the Study of Pain® (IASP®). Hicks CL, et al. The Faces Pain Scale – Revised: toward a common metric in pediatric pain measurement. Pain. 2001;93:173-183.

Numerical Rating Scale (NRS) For Children ≥ 8 Years and Adults

Pain: "Tell me how much pain/hurt you had from the vaccine injection from 0 to 10, where 0 is no pain/hurt and 10 is worst pain/hurt possible."
Fear: "Tell me how scared you were during the vaccine injection from 0 to 10, where 0 is not scared at all and 10 is the most scared possible."

Fear Verbal Descriptor Scale for Children 5-12 Years*

Tell me how scared you were during the needle: not at all, a little bit, a medium amount, a lot, or very very much/most possible?

Children's Fear Scale (CFS) for Children 5-12 Years*

These faces are showing different amounts of being scared. This face *[point to the left-most face]* is not scared at all, this face is a little bit more scared *[point to second face from left]*, a bit more scared *[sweep finger along scale]*, right up to the most scared possible *[point to the last face on the right]*. Have a look at these faces and choose the one that shows how scared you were during the needle.

(Score the faces from 0 on the far left to 4 on the far right)

Figure reproduced with permission of the author. http://pphc.psy.uoguelph.ca/index.php/the-childrens-fear-scale/
McMurtry CM, et al. Children's fear during procedural pain: preliminary invesigation of the Children's Fear Scale. Health Psychology. 2011;30:780-788.

Faces Anxiety Scale (FAS) for Critically ill Adults

These faces are showing different levels of anxiety. This face shows no anxiety at all, this face shows a little bit more, a bit more *[sweep finger along scale]*, right up to extreme anxiety. Have a look at these faces and choose the one that shows how much anxiety you felt during the needle.

(Score the faces from 1 on the far left to 5 on the far right)

Figure reproduced from Journal of Advanced Nursing 41, McKinley S, Coote K, Stein-Parbury J, Development and testing of a faces scale for the assessment of anxiety in critical ill patients, 73-79, Copyright 2003, with permission from Wiley.

*Children < 7 years may not be reliable in their self-report; ratings from multiple people are recommended (e.g., caregivers, healthcare providers, child)

Health Care Provider Intervention Documentation Tool

Use this document to track pain mitigation strategies used during vaccination and their effectiveness. Use this to prepare for the next vaccination.

Name of individual:	Infants					Toddlers		School Age	Adolescents > 12 - 17 years					Adults		Other Vaccinations (flu, travel...)		
	Birth	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4-6 years	Age:	Age:	Age:	Age:	Age:	Age:	Age:	Age:	Age:	Age:
Vaccines Administered																		
Interventions:																		
Caregiver presence	☐	☐	☐	☐	☐	☐	☐	☐								☐	☐	☐
Breastfeeding OR	☐	☐	☐	☐	☐	☐	☐									☐	☐	☐
Sweet tasting solution	☐	☐	☐	☐	☐	☐	☐									☐	☐	☐
Positioning: skin to skin contact	☐															☐	☐	☐
holding	☐	☐	☐	☐	☐	☐	☐									☐	☐	☐
Non-nutritive sucking	☐	☐	☐	☐	☐	☐	☐									☐	☐	☐
Topical anesthetic	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Injection without aspiration	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Multiple injections: most painful vaccine last AND/OR	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Simultaneous injection	☐	☐	☐	☐	☐											☐	☐	☐
Inject in vastus lateralis	☐	☐	☐	☐												☐	☐	☐
Positioning - upright/sitting								☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Distract – toy, video	☐	☐	☐	☐	☐	☐	☐									☐	☐	☐
Distract - music, video, breathe with toy, verbal distraction								☐								☐	☐	☐
Vibrating device with cold								☐	☐	☐	☐	☐	☐			☐	☐	☐
Breathing method - cough, breathhold														☐	☐	☐	☐	☐
Vapocoolant spray														☐	☐	☐	☐	☐
Neutral verbal signal of procedure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Muscle Tension (if history of fainting)									☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post-vaccination assessments (age-appropriate):																		
Provider-rated distress: MBPS (child ≤18 months); FLACC (child >18 months); r-FLACC (child with cognitive impairment/CI); CNPI (adults with CI)																		
Scale 0-10 (MBPS, FLACC/r-FLACC)																		
Scale 0-6 (CNPI)																		
Parent-rated distress: NRS or VAS (child ≤ 3 years or child with CI); (NCCPC-PV for parents of children with CI available at pediatric-pain.ca/our-measures)																		
Scale 0-10 (NRS, VAS)																		
Scale 0-81 (NCCPC-PV)																		
Child self-reported pain: Pieces of Hurt Tool (child 3-6 years); FPS-R (child ≥ 5 years); NRS (child ≥ 8 years)																		
Scale 0-4 (Pieces of Hurt)																		
Scale 0-10 (FPS-R, NRS)																		
Child self-reported fear: CFS or verbal descriptor scale (child 5-12 years); NRS (child ≥ 8 years)																		
Scale 0-4 (CFS, descriptor)																		
Scale 0-10 (NRS)																		
Adult self-reported pain: NRS																		
Scale 0-10																		
Adult self-reported fear: NRS; FAS (critically ill adults)																		
Scale 0-10 (NRS)																		
Scale 1-5 (FAS)																		

* MBPS = Modified Behavioural Pain Scale (0-10); FLACC = Face Legs Activity Cry Consolability and r-FLACC = revised version (0-10); NCCPC-PV: Noncommunicating Children's Pain Checklist-Postoperative version 0-81; CNPI = Checklist of Nonverbal Pain Indicators; CI = cognitive impairment; NRS = Numerical Rating Scale (0-10); VAS = Visual Analog Scale (0-10); Pieces of Hurt Tool (0-4); FPS-R = Faces Pain Scale - Revised (0-10); CFS = Children's Fear Scale (0-4); FAS = Faces Anxiety Scale (1-5). See reverse side for description of these scales and scores; NCCPC-PV available separately at pediatric-pain.ca/our-measures

Fainting response? Prodromal - dizzy, light headed, nauseated, sweaty. Actually fainted?																		
Prodromal? Fainted?																		

Comparison of original 2010 and 2015 Clinical Practice Guideline

2010 Clinical Practice Guideline	2015 Clinical Practice Guideline
Scope and Purpose	
Vaccine injections in childhood	Vaccine injections across the lifespan
Recommendations	
1. Procedural interventions	
Guidance regarding order of vaccine injections	Additional guidance across the lifespan
Guidance regarding aspiration and speed of injection	Additional guidance across the lifespan; *Removal of guidance regarding speed*
Guidance regarding simultaneous injections	Additional guidance across the lifespan
Guidance regarding brand of vaccine and tissue (intramuscular vs. subcutaneous) injected	*Removal of guidance*
	Additional guidance regarding body region for vaccine injection in infants
2. Physical Interventions	
Guidance on positioning	Additional guidance, including additional interventions, across the lifespan
Guidance on breastfeeding in infants	Additional guidance, including additional interventions, extension of age
Guidance regarding manual tactile stimulation	Additional guidance for vibrating devices; *Removal of manual tactile stimulation*
Guidance regarding vapocoolants	Additional guidance across the lifespan;

	Age-specific recommendations
Guidance regarding ice	*Removal of guidance*
	Additional guidance for warming the vaccine, non-nutritive sucking, muscle tension
3. Pharmacological Interventions	
Guidance regarding topical anesthetics	Additional guidance across the lifespan
Guidance regarding oral analgesics	Additional guidance across the lifespan
Guidance regarding sweet-tasting solutions in infants	Additional guidance, including additional interventions, extension of age
4. Psychological Interventions	
Guidance regarding clinician-led, parent-led and child-led distraction, parent coaching, breathing interventions, and combined psychological interventions	Additional guidance across the lifespan and separation of recommendations according to type of distraction; *Age-specific recommendations*
Guidance regarding interactions – use of suggestion	Additional guidance across the lifespan; Expanded to include reassurance and neutral language to signal impending procedure
5. Process Interventions	
	Additional guidance regarding education of clinicians, parents, individuals across the lifespan
	Additional guidance regarding parent presence during childhood vaccinations

6. Other	
	Additional guidance regarding specific combinations of interventions; e.g., breastfeeding and topical anesthetics
	Additional guidance regarding exposure therapy and applied tension in individuals with high levels of needle fear*

* Published separately (McMurtry et al., under review)[34]