



Individuals who have been diagnosed with blood-injection-injury phobia (ie, the type of specific phobia that needle phobia falls within in the Diagnostic and Statistical Manual of Mental Disorders—5th Edition<sup>17</sup>) are at the severe end of the needle fear spectrum. The lifetime prevalence of blood-injection-injury phobia is approximately 3% to 4.5%.<sup>3,18,19</sup> The prevalence rises when individuals who have a high degree of needle fear, but not a diagnosis of needle-related phobia, are considered (estimated at approximately 10% of the population).<sup>4-6,12</sup> It is important to note that individuals who have not been diagnosed with a needle phobia or who would be considered below the diagnostic threshold for the disorder are nevertheless at increased risk for adverse outcomes. Indeed, they may have sufficiently elevated levels of anxiety and fear about needles that lead to the avoidance of procedures entirely, their responses interfere with clinicians' ability to carry out procedures (eg, due to fainting, flailing, attempts to escape), or their fear impedes the efficacy of traditional interventions for procedural pain.<sup>12,15,20</sup> Individuals with high levels of needle fear who also have chronic health conditions requiring injections (eg, diabetes) are a particularly vulnerable group who require treatment of their fear to maximize adherence to their medical regimen and avoid negative health effects.<sup>6,15,21,22</sup>

In 2010, a multidisciplinary team from across Canada published a clinical practice guideline on the management of vaccination pain in infants and children.<sup>23</sup> In 2013, HELPinKIDS 2.0 (herein, HELPinKids&Adults) was launched to address stakeholders' interest in an update of the knowledge synthesis to: (1) include trials that had been published after 2010; (2) broaden the scope to include adults; and (3) provide guidance on the management of high levels of needle fear. It was recognized by this team that individuals with a high degree of needle fear present a significant challenge to front line immunizers and that traditional vaccination pain management strategies were not appropriate for this particularly vulnerable population.

Interventions that hold particular promise for reducing needle fears, as well as associated responses such as fainting, in this highly fearful or phobic group of individuals are exposure and applied tension (ie, muscle tension + exposure). Exposure is a psychological intervention that is considered an efficacious treatment for specific phobias in general<sup>24-27</sup> and may be delivered in various formats (eg, in vivo, imaginal, single session, multiple session). Exposure-based therapy involves a hierarchical presentation of the feared stimulus. For needle procedures, aspects of needle procedures would be encountered in a hierarchical manner of ascending fear (eg, sitting in the waiting room, to seeing a syringe without a needle, to seeing a syringe with a needle, to holding a syringe with a needle, to holding the tip of a needle against one's arm, and culminating in receipt of an injection). Exposure-based therapy also frequently includes instruction, participant modeling, and targeting of catastrophic thoughts (ie, cognitive distortions or thinking errors, such as magnifying the threat of the needle) made by the individual. The exposure must be of a sufficient duration that the individual's fear decreases, he or she realizes the "catastrophe" did not occur, or that he or she can survive it (tests the catastrophic belief).<sup>28</sup>

Although phobias are often considered as a homogeneous group, this may be an oversimplification and obscure important differences with implications for treatment, particularly for fear relating to needles. For example, individuals with high levels of needle fear or blood-injection-injury phobia have an increased risk of showing a

vasovagal response (fainting) when confronting the feared situation<sup>3,5,10,11,29</sup>; indeed, this response is not seen in other specific phobias. The vasovagal response is typically described as diphasic (but see Ritz et al<sup>30</sup>); specifically, an increase in blood pressure and heart rate is followed by an overcompensatory, precipitous decrease in blood pressure and heart rate leading to reduced cerebral blood flow and eventual loss of consciousness (fainting). Muscle tension is a physical technique in which individuals are taught to: (1) tense their muscles (eg, abdominal, legs, arms) to raise their blood pressure and combat the vasovagal response; (2) recognize prodromal signs of impending vasovagal syncope (eg, visual disturbances, feeling dizzy, or clammy); and (3) apply the technique when prodromal signs occur.<sup>31</sup> Muscle tension becomes "applied tension" when individuals practice the technique while being exposed to the object of their fear (eg, needles). This technique has been recommended to reduce fainting during voluntary blood donations<sup>32</sup> and has also been investigated within the context of needle fear and fainting.<sup>30,33</sup>

There are narrative reviews on blood-injury phobia<sup>7,13</sup> (as conceptualized in the Diagnostic and Statistical Manual of Mental Disorders-III<sup>34</sup>), blood-injection-injury phobia<sup>6,10,11,14</sup> as well as injection phobia.<sup>35</sup> Ayala et al<sup>33</sup> published a more recent systematic review focused on the efficacy of applied tension for adults with blood-injection-injury phobia but did not provide a full meta-analysis. The aforementioned reviews also focused almost exclusively on adult populations with 2 exceptions, one of which is a brief commentary,<sup>36</sup> whereas the other is a narrative review.<sup>14</sup> Although the reviews typically list a variety of treatments that have been utilized for needle fear and needle phobia (eg, exposure, systematic desensitization, modeling, relaxation training, education, reassurance, pharmacological strategies including conscious sedation and anxiolytics, distraction, hypnosis, general cognitive-behavioral strategies, family interventions<sup>6,7,10,11,13,14,35</sup>), none have provided a systematic review and full meta-analysis of treatments in the context of the quality of the original studies. Furthermore, the management of these fears has never been reviewed in relation to the vaccination context. In sum, given the frequency of needle procedures, the consequences of unmitigated pain and fear,<sup>20</sup> and the lack of systematic treatment evaluation, there is a clear and urgent need to systematically synthesize the literature on the treatment of high levels of needle fear, including, but not limited to, needle phobia.

The current systematic review synthesized the evidence for the following exposure-based, behavioral interventions with respect to management of needle fear in children and adults: (1) in vivo exposure (graduated exposure to the actual feared stimulus); (2) multiple versus single sessions of in vivo exposure; and (3) non in vivo exposure (indirect exposure to the feared stimulus using computer-based stimuli or individuals' imaginations). In addition, applied tension (muscle tension with exposure) versus exposure alone was evaluated for reducing fainting among individuals with high needle fears.

## METHODS

The current systematic review is part of a series of reviews using consistent search strategy, data extraction and pooling, and quality assessment processes following both the Grading of Recommendations Assessment,

TABLE 1. Clinical Questions and Outcomes

Clinical Questions	Critical Outcomes	Important Outcomes
<b>Interventions for individuals with high needle fear</b>		
Should in vivo exposure-based therapy be used for children $\geq 7$ y with high levels of needle fear?	Fear	Distress, pain, fainting, procedure outcomes, parent fear, compliance, memory, preference, satisfaction
Should in vivo exposure-based therapy be used for adults with high levels of needle fear?	Fear	Distress, pain, fainting, procedure outcomes, compliance, memory, preference, satisfaction
Should multiple-session in vivo exposure-based therapy be used (rather than single session) for children $\geq 7$ y and adults with high levels of needle fear?	Fear	Distress, pain, fainting, procedure outcomes, compliance, memory, preference, satisfaction
Should non in vivo (imaginal) exposure-based therapy be used for children $\geq 7$ y with high levels of needle fear?	Fear	Distress, pain, fainting, procedure outcomes, parent fear, compliance, memory, preference, satisfaction
Should non in vivo exposure-based therapy be used for adults with high levels of needle fear?	Fear	Distress, pain, fainting, procedure outcomes, compliance, memory, preference, satisfaction
Should applied tension (exposure and muscle tension) be used for children $\geq 7$ y and adults with high levels of needle fear and fainting?	Fainting	Fear, distress, pain, procedure outcomes, compliance, memory, preference, satisfaction

Development and Evaluation (GRADE<sup>37</sup>) and Cochrane methodologies.<sup>38</sup> Details of the overarching methodology are provided elsewhere.<sup>39</sup> Briefly, the HELPinKids&Adults Team was brought together to update and expand a previous knowledge synthesis and clinical practice guideline and provide cutting edge guidance on the management of vaccination pain across the lifespan as well as the management of high levels of needle fear. Consistent with the GRADE process, the selection of clinical questions and rating of the importance of outcomes was achieved using a team-based voting approach (described in detail in Taddio et al<sup>39</sup>). The systematic search strategy was developed by evidence leads under the guidance of a librarian with expertise in systematic reviews. The following databases were searched: EMBASE, Medline, PsycINFO, CINAHL, and ProQuest Dissertations & Theses Global. This broad search strategy yielded a large number of results that were screened for eligibility.<sup>39</sup> Articles of potential interest to the current systematic review were then screened again by 2 reviewers (C.M.M. and D.L., a research assistant). Included articles were extracted in full on customized forms by the lead author (C.M.M.) and checked by the second author (M.N.).

The inclusion criteria for the current systematic review were as follows: (1) participants were individuals with a high degree of needle fear or phobia related to needles such as blood-injection-injury phobia or injection phobia (in the absence of data for individuals with needle fear, other specific phobias were accepted) undergoing vaccination or next closest procedure; (2) a randomized or quasi-randomized trial examining exposure-based interventions with at least 5 participants per group; (3) measurement of an outcome of interest; and (4) published report (short or full) or published academic thesis. Of note, the inclusion of individuals with non-needle-related specific phobias (eg, spider) occurred solely for the clinical questions regarding children. The pediatric treatment literature typically collapses across phobia subtypes (this was done in 3 of the 6 included trials; these trials had the largest numbers of participants<sup>40-42</sup>) and exposure-based treatments have been recommended for specific phobias in general.<sup>24,25</sup> The foci of fear of participants of included trials are described within each clinical question.

Critical outcomes (as voted upon by the HELPinKids&Adults Team) were specific fear (ie, fear particular to the situation, object, or both that is the focus of the

individual's apprehension; ideally, this would be needle fear but could be, for example, fear of spiders in individuals diagnosed with a phobia of spiders) for the questions relating to exposure therapy and fainting for the remaining question on applied tension. Specific fear was typically measured through multi-item questionnaires or using a rating of acute fear during an imagined or actual engagement with the feared stimulus as part of a behavioral avoidance test (described below). Important outcomes included: general fear (global apprehension regarding a host of situations and objects), compliance, parent fear, pain, distress, procedure outcomes, memory, and preferences. General fear was also measured through multi-item questionnaires. It is important to note that given the targeted nature of exposure-based interventions to the specific feared stimulus, a reduction in general fear is not necessarily expected. A behavioral avoidance test or BAT (also known as a behavioral approach test or task [The term "behavioral avoidance test" was chosen for consistency with Öst's terminology; his work comprises much of the review.]) was typically used to measure compliance; in a BAT, the individual is asked to complete successive steps or tasks of engagement with the feared stimulus and is scored according to the number or percentage of steps successfully completed. Fainting was measured by observer report of fainting behavior during a BAT. Where possible, analyses were separated by age (children vs. adults). Table 1 presents the included clinical questions as well as critically important and important outcomes included in the review.

If more than 1 indicator of an outcome was available (eg, 2 or more questionnaires on specific fear), they were combined using established approaches before meta-analysis.<sup>43</sup> As part of each article extraction, Cochrane's risk of bias tool (<https://bmg.cochrane.org/assessing-risk-bias-included-studies>) was applied on an outcome level. Data were pooled using the RevMan software program (version 5.2, Cochrane Collaboration, Copenhagen, Denmark) using a random effects model; standardized mean difference (SMD) for continuous data or relative risk for dichotomous data along with 95% confidence intervals (CI) were used to assess the effectiveness of an intervention. If data were unavailable in the published paper, efforts were made to contact the authors for more information, or calculations were made from available data on a restricted basis using accepted formulae (eg, means and SDs were calculated

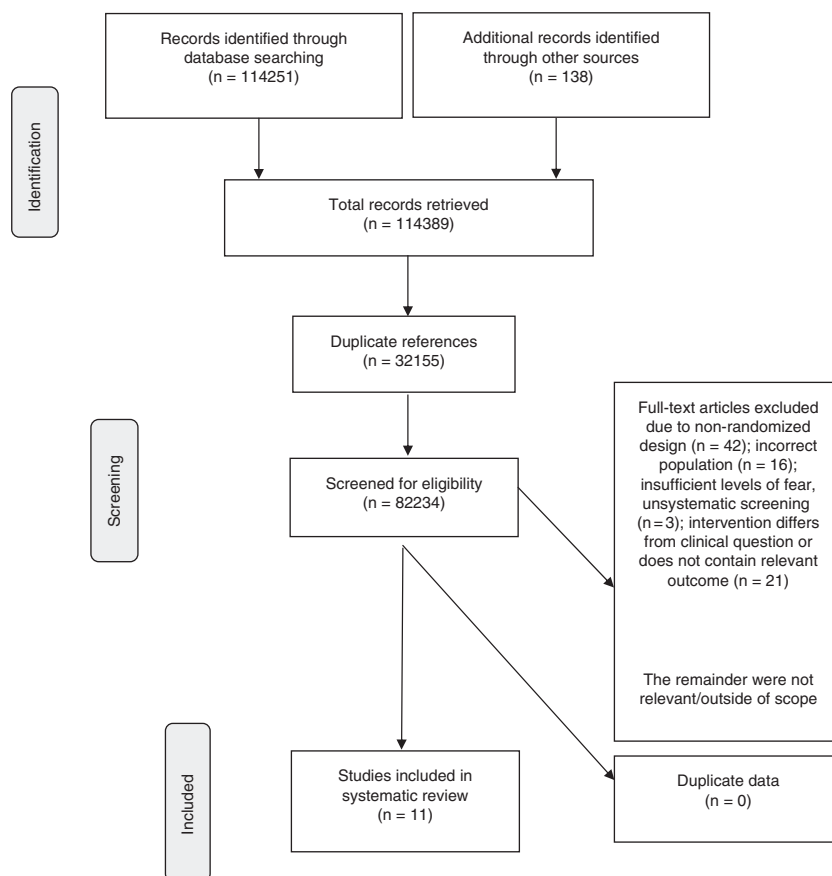


FIGURE 1. Flow of studies.

from medians and ranges) or estimated from graphs.<sup>44</sup>  $I^2$  and  $\chi^2$  tests were used to assess statistical heterogeneity. The GRADE assessment of quality was used to summarize quality across studies using the GRADE profiler software (version 3.6.1); footnotes were used as explanatory aids.

## RESULTS

Figure 1 shows the flow of studies from database searching to inclusion in the current review. Eleven studies examining exposure-based treatments were retained for inclusion in the review and are described in Table 2. Six of the included trials focused on children, with the remainder enrolling adults only. One of the trials<sup>46</sup> used a crossover design. However, only data from after completion of the first treatment were retained and, as a consequence, the included data represent a parallel, between-groups design. The remaining 10 trials<sup>40–42,45,47–52</sup> used a parallel groups design with at least 2 treatment arms; for the 3 trials which used waitlist control groups that received treatment before the long-term follow-up, only data collected before the waitlist control group was randomized to active treatments were included in analyses.<sup>40–42</sup>

Notable sources of exclusion were as follows (note that some citations could fall within more than 1 category but for clarity of reporting are described in the most applicable category): (1) nonrandomized design including case studies investigating exposure-based interventions (n = 37)<sup>21,53–88</sup> or case series (n = 5)<sup>31,89–92</sup>; (2) incorrect population including

RCTs with children with nonspecific phobias (n = 2; eg, social phobia, agoraphobia)<sup>93,94</sup> or adults with general or global dental fear, which is seen as a distinct issue<sup>29</sup> (n = 2)<sup>95,96</sup>; (3) incorrect population including muscle tension techniques explored in nonfearful populations (n = 3),<sup>97–99</sup> as well as a series of studies examining the muscle tension technique in voluntary blood donors (individuals who would volunteer to give blood are seen as unlikely to have high levels of needle fear<sup>100</sup>; n = 9)<sup>101–109</sup>; (4) insufficient levels of fear, unsystematic screening process, or the potential that the fear was adaptive (ie, presence of a fear of water when it was unclear whether participants knew how to swim; n = 3)<sup>110–112</sup>; and (5) treatment did not match clinical questions, dismantling trials, or no relevant outcomes (n = 21).<sup>113–133</sup>

## Quality of Studies and Risk of Bias

The risk of bias assessment (Cochrane methodology) for each trial is shown in Table 3. All of the included trials had a high risk of bias, which was primarily due to lack of blinding of participants, personnel, and outcome assessor. Generally, there were also insufficient descriptions of sequence generation and allocation concealment to permit judgment. Other potential sources of bias are noted using footnotes.

## Overall Quality of Evidence and Treatment Effects

A quantitative review of the effects of each intervention is provided below, organized by clinical question. Only the

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

Author Year, Country	Procedure/ Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes
<b>Should in vivo exposure-based therapy be used for children ≥ 7 y with high levels of needle fear?</b>				
Flatt 2010, <sup>40</sup> Australia	NA 10-step BAT for particular object of fear	N = 43 7-17 y Object of fear: various (n = 6 with fear of needles; DSM-IV specific phobia); between- groups design*; single center, unclear setting	In vivo exposure: 1 session ≤ 3 h; modeling, hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs, contingency management, relaxation training; delivered by a psychologist (n = 17) or Psychoeducation and supportive psychotherapy: length, number of sessions unclear; talking about fears, learning differences between fear, anxiety and phobias, learning etiology of phobias, targeting enhancement of self-efficacy, discussion of exposure (but no actual exposure); delivered by a psychologist (n = 15)† or Waitlist control (n = 11)*	NA (this study was not included in the meta-analysis for critical outcomes)
Leutgeb 2012, <sup>45</sup> Austria	NA Viewing a series of pictures of spiders	N = 32 8-13 y Object of fear: spiders (DSM-IV specific phobia); between- groups design; single center, unclear setting	In vivo exposure: 1 session ≤ 4 h; psychoeducation, modeling, hierarchical exposure to feared stimuli, cognitive restructuring; delivered by a psychologist (n = 15) or Waitlist control (n = 17)	Specific fear: SPQ-C, SAM
Muris 1998 (1), <sup>46</sup> the Nether- lands	NA 10-step spider BAT	N = 26 8-17 y Object of fear: spiders (DSM-III-R simple phobia); between-groups design‡; single center, university	In vivo exposure: 1, 2.5 h session; rationale, modeling, hierarchical exposure to feared stimuli; delivered by a behavioral scientist (n = 9) or Eye-movement desensitization and reprocessing: 1, 2.5 h session; imaginal exposure + horizontal eye movements with cognitive restructuring; delivered by a therapist (n = 9)† or Placebo: 1, 2.5 h session; computerized exposure to feared stimuli (n = 8)§	Specific fear: SPQ-C short form, SAM- Spider, BAT-SAM
Ollendick 2009, <sup>41</sup> Sweden and United States	NA BAT for particular object of fear	N = 196 7-16 y Object of fear: various but excluded blood-injection injury (DSM-IV specific phobia); between-groups design*; multicenter, unclear setting	In vivo exposure: 1 session ≤ 3 h; instruction, modeling, hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs; delivered by therapists (n = 85) or Education support therapy: 1 session ≤ 3 h; learning definition of fear and phobia, etiology of phobias, physiological components, description of “slipping” and how to handle it; delivered by therapists (n = 70)† or Waitlist control (n = 41)*	Specific fear: BAT- fear
Öst 2001 (1, 2), <sup>42</sup> Sweden	NA BAT for particular object of fear	N = 60 7-17 y and parents in 1 group Object of fear: various (n = 12 for injections, n = 2 blood; DSM- IV specific phobia); between- groups design*; single center, unclear setting	In vivo exposure child alone: 1 session ≤ 3 h; instruction, modeling, hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs; delivered by psychologists (n = 21) or In vivo exposure child and parent: 1 session ≤ 3 h; instruction, modeling, hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs; delivered by psychologists (n = 20) or Waitlist control (n = 19)*	Specific fear: BAT- fear
<b>Should in vivo exposure-based therapy be used for adults with high levels of needle fear?</b>				
Öst 1991 (1), <sup>47</sup> Sweden	NA Surgical film BAT	N = 30 18-55 y Object of fear: blood-injection- injury (DSM-III-R simple phobia); between-groups	In vivo exposure: 5 weekly 45 min to 1 h sessions; rationale for technique, hierarchical exposure to feared stimuli; delivered by graduate students (n = 10) or	Specific fear: MQ, FSS-III-Blood, FQ- Blood/injury, BAT- Fear

(Continued)

TABLE 2. (continued)

Author Year, Country	Procedure/ Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes
		design; single center, outpatients of a mental hospital but unclear setting	Muscle tension: 5 weekly 45 min to 1 h sessions; rationale for technique, practice of technique without exposure to feared stimuli; delivered by graduate students (n = 10) or Muscle tension + in vivo exposure (applied tension): 5 weekly 45 min to 1 h sessions; rationale for technique; practice technique without exposure then with hierarchical exposure to feared stimuli; delivered by graduate students (n = 10)†	
<b>Should multiple-session in vivo exposure-based therapy be used (rather than single session) for children ≥ 7 y and adults with high levels of needle fear?</b>				
Öst 1992, <sup>48</sup> Sweden	20-step venipunc- ture BAT	N = 40 18-51 y Object of fear: injections (DSM-III-R simple phobia); between-groups design; single center, outpatients of a mental hospital but unclear setting	Single session in vivo exposure: 1 session ≤ 3 h; preparation, rehearsal, hierarchical exposure to feared stimuli; delivered by psychologists (n = 20) or Multiple-session in vivo exposure: 5 weekly 1 h sessions; preparation, rehearsal, hierarchical exposure to feared stimuli; delivered by psychologists (n = 19)	Specific fear: IPS, MQ, FSS-III-Injection, BAT-Fear
Vika 2009, <sup>49</sup> Norway	13-step dental injection BAT	N = 55 18-62 y Object of fear: intraoral injections (DSM-IV specific phobia); between-groups design; single center, university	Single session in vivo exposure: 1 session (length NR); hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs; delivered by dentists (n = 28) or Multiple-session in vivo exposure: 5 weekly 1 h sessions; hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs; delivered by dentists (n = 26)	Specific fear: IPS-Anxiety, MQ, BAT-Fear
<b>Should non in vivo (imaginal) exposure-based therapy be used for children ≥ 7 y with high levels of needle fear?</b>				
Cornwall 1996, <sup>50</sup> Australia	NA A darkness tolerance test (BAT)	N = 24 7-10 y Object of fear: darkness (DSM-III-R simple phobia); between-groups design; single center, university psychology clinic	Emotive imagery: 6 weekly 40 min sessions; variant of hierarchical imaginal exposure (includes imagining presence of a "superhero"); delivered by a psychologist (n = 12) or Waitlist control (n = 12)	Specific fear: Fear Thermometer, FSSC-R-Unknown
Muris 1998 (2), <sup>46</sup> the Nether- lands	NA 10-step spider BAT	N = 26 8-17 y Object of fear: spiders (DSM-III-R simple phobia); between-groups design‡; single center, university	In vivo exposure: 1, 2.5 h session; rationale, modeling, hierarchical exposure to feared stimuli; delivered by a behavioral scientist (n = 9)† or Eye-movement desensitization and reprocessing: 1, 2.5 h session; imaginal exposure + horizontal eye movements with cognitive restructuring; delivered by a therapist (n = 9) or Placebo: 1, 2.5 h session; computerized exposure to feared stimuli (n = 8)§	Specific fear: SPQ-C short form, SAM-Spider, BAT-SAM
<b>Should non in vivo exposure-based therapy be used for adults with high levels of needle fear?</b>				
Heaton 2013, <sup>51</sup> United States	Receipt of dental injection after treatment	N = 84 18-68 y Object of fear: dental injections and needles (assessed by 2 questionnaires); between-groups design; multicenter, dental clinics	Computer exposure: 9 video segments of CARL program; completed in 1-3 45 min sessions; relaxation training, cognitive distraction, positive coping strategies, then hierarchical exposure to feared stimuli with modeling (n = 34) or Educational pamphlet: information about comfort, anesthetics, postoperative pain management (control) (n = 34)	Specific fear: MISAR, NS
Mohr 2005, <sup>52</sup> United States	Self-injection of medication	N = 30 18-61 y with multiple sclerosis Object of fear: injections (inability to self-inject medication)	Imaginal exposure: 6 weekly sessions (length NR) of SIAT; psychoeducation, progressive muscle relaxation, hierarchical imaginal exposure and relaxation (systematic desensitization) to feared	NA (this study was not included in the meta-analysis for critical outcomes)

(Continued)

TABLE 2. (continued)

Author Year, Country	Procedure/ Injection Details	Population Enrolled, Design, Setting	Intervention	Critical Outcomes
		≥ 3 mo; 12/30 met DSM-IV specific phobia of blood-injection-injury); between-groups design; university multiple sclerosis center	stimuli, cognitive restructuring, in vivo attempt of injection in fourth and fifth sessions; delivered by nurses (n = 15) or Telephone support: 6 wk (length NR) of education on injection techniques and progressive muscle relaxation; delivered by nurses (n = 15)	
<b>Should applied tension (exposure and muscle tension) be used for children ≥ 7 y and adults with high levels of needle fear and fainting?</b>				
Öst 1991 (2), <sup>47</sup> Sweden	NA Surgical film BAT	N = 30 18-55 y Object of fear: blood-injection-injury (DSM-III-R simple phobia); between-groups design; single center, outpatients of a mental hospital but unclear setting	In vivo exposure: 5 weekly 45 min to 1 h sessions; rationale for technique, hierarchical exposure to feared stimuli; delivered by graduate students (n = 10) or Muscle tension: 5 weekly 45 min to 1 h sessions; rationale for technique, practice of technique without exposure to feared stimuli; delivered by graduate students (n = 10) <sup>†</sup> or Muscle tension + in vivo exposure (applied tension): 5 weekly 45 min to 1 h sessions; rationale for technique; practice technique without exposure then with hierarchical exposure to feared stimuli; delivered by graduate students (n = 10)	Specific fear: MQ, FSS-III-Blood, FQ-Blood/injury, BAT-Fear

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

\*Data for waitlist control only available at posttreatment time-point; waitlist control randomized to active treatment condition(s) before longer term follow-up. Only data before waitlist control randomization into active condition(s) were included, thus design is considered parallel (between-groups).

†These data were not included in analyses for this question.

‡Only between-groups data following the completion of the first treatment were included (ie, omitted crossover data collected after all groups received traditional exposure treatment).

§Muris et al<sup>46</sup>: the authors considered the computer-based exposure treatment to be a placebo or control group; however, this is problematic.

Intervention: CARL, Computer Assisted Relaxation Learning; SIAT, Self-Injection Anxiety Therapy. Outcomes: BAT, Behavioral Avoidance Test (also known as a Behavioral Approach Test or Task); BAT-SAM, Self-Assessment Manikin during the Behavioral Avoidance Test; FQ-Blood/injury, Fear Questionnaire—Blood/injury subscale; FSS-III-Blood, Fear Survey Schedule Third Edition—Blood subscale; FSS-III-Injection, Fear Survey Schedule Third Edition—Injection item; FSS-R-Unknown, Fear Survey Schedule Revised—Fear of the Unknown subscale; IPS, Injection Phobia Scale; IPS-Anxiety, Injection Phobia Scale—Anxiety subscale; MISAR, Modified Interval Scale of Anxiety Response; MQ, Mutilation Questionnaire; NS, Needle Survey; SAM, Self-Assessment Manikin; SAM-Spider, fear of spiders in general; SPQ-C, Spider Phobia Questionnaire for Children. Other: NA, not applicable; NR, not reported.

results of critical outcomes are reported in text; however, the important outcomes for which data are available are named to guide readers. All results for both critically important and important outcomes are included as Supplemental Digital Content including GRADE Evidence Profiles and Summary of Findings tables (Tables, Supplemental Digital Content 1 to 6, <http://links.lww.com/CJP/A225>, <http://links.lww.com/CJP/A226>, <http://links.lww.com/CJP/A227>, <http://links.lww.com/CJP/A228>, <http://links.lww.com/CJP/A229>, <http://links.lww.com/CJP/A230>) and accompanying Forest plots (Figures, Supplemental Digital Content 7 to 12, <http://links.lww.com/CJP/A231>, <http://links.lww.com/CJP/A232>, <http://links.lww.com/CJP/A233>, <http://links.lww.com/CJP/A234>, <http://links.lww.com/CJP/A235>, <http://links.lww.com/CJP/A236>). It is important to note that no trials were identified that were specific to vaccine injections. Table 4 presents a summary of the findings for critical outcomes.

**Should In Vivo Exposure-based Therapy be Used for Children 7 Years and Above With High Levels of Needle Fear?**

No trials were identified that: (1) examined in vivo exposure-based therapy specifically for children with high

levels of needle fear (including blood-injection-injury phobia), or (2) reported results separately for children with needle-related fear. Thus, 5 trials<sup>40-42,45,46</sup> with 263 children aged 7 to 17 years meeting diagnostic criteria for a specific phobia according to the edition of the Diagnostic and Statistical Manual of Mental Disorders current at the time of the study were included in the analysis. In Flatt and King,<sup>40</sup> 6 of 43 participants had a fear of needles, whereas in Öst et al,<sup>42</sup> 12 of the 60 participants had a fear of injections and 2 had a fear of blood; the remaining participants had a variety of specific phobias including spiders,<sup>45,46</sup> enclosed spaces, or animals.<sup>41,42</sup> One study<sup>41</sup> excluded participants with blood-injection-injury phobia.

Treatment was delivered in a single session ranging between 2.5 and 3 hours in 4 of the studies<sup>40-42,46</sup> and 4 hours in the remaining study.<sup>45</sup> All the treatments were modeled after Öst’s<sup>28</sup> “One session treatment” and included modeling and hierarchical exposure to the feared stimuli; 4 of the trials<sup>40-42,45</sup> specified some degree of cognitive restructuring or targeting of the catastrophic cognition. Comparison groups were waitlist control<sup>40-42,45</sup> or a “placebo” group of a computerized exposure to spiders.<sup>46</sup> In vivo exposure-based therapy demonstrated benefit on specific fear (4 trials; n = 235; SMD: - 1.71 [95% CI:

–2.72, –0.7]) (Table, Supplemental Digital Content 1, <http://links.lww.com/CJP/A225> and Figure, Supplemental Digital Content 7, <http://links.lww.com/CJP/A231>). Important outcomes with data shown in the supplemental digital content (Table, Supplemental Digital Content 1, <http://links.lww.com/CJP/A225> and Figure, Supplemental Digital Content 7, <http://links.lww.com/CJP/A231>) include general fear, compliance (using a BAT), child satisfaction, and parent satisfaction.

### Should In Vivo Exposure-based Therapy be Used for Adults With High Levels of Needle Fear?

One trial with 20 adult participants diagnosed with blood-injection-injury phobia (excluding those with only an injection phobia) according to the DSM-III-R<sup>134</sup> was included in this analysis.<sup>47</sup> Treatment was given in 5 weekly sessions of approximately 45 minutes and included hierarchical exposure to the feared stimuli. The comparison group was trained in muscle tension but did not undergo exposure. In vivo exposure-based therapy showed benefit on specific fear posttreatment ( $n = 20$ ; SMD:  $-1.09$  [ $-2.04, -0.14$ ]) but not at 1-year follow-up ( $n = 20$ ; SMD:  $-0.28$  [ $-1.16, 0.6$ ]) (Table, Supplemental Digital Content 2, <http://links.lww.com/CJP/A226> and Figure, Supplemental Digital Content 8, <http://links.lww.com/CJP/A232>). Important outcomes with data shown in the supplemental digital content (Table, Supplemental Digital Content 2, <http://links.lww.com/CJP/A226> and Figure, Supplemental Digital Content 8, <http://links.lww.com/CJP/A232>) include each of the following at posttreatment and 1-year follow-up: general fear, fainting, and compliance (using a BAT).

### Should Multiple-session In Vivo Exposure-based Therapy be Used (Rather Than Single Session) for Children 7 Years and Above and Adults With High Levels of Needle Fear?

Two trials with 93 adults who were fearful of injections were included in this analysis comparing multiple and single sessions of in vivo exposure.<sup>48,49</sup> Participants met the diagnostic criteria for specific phobia according to the version of the Diagnostic and Statistical Manual of Mental Disorders that was in use at the time of the study. According to study descriptions, both treatments followed Öst's treatment principles<sup>28,42</sup>; in vivo exposure consisted of either preparation, rehearsal, hierarchical exposure to feared stimuli,<sup>48</sup> or hierarchical exposure to feared stimuli targeting focus of catastrophic beliefs.<sup>49</sup> Multiple-session in vivo exposure was given over 5 weekly 1 hour sessions in both trials; the 1 session treatment was maximized to 3 hours in 1 trial<sup>48</sup> but the length of time was not reported for the other trial.<sup>49</sup> Results were mixed for the critical outcome of specific fear (Table, Supplemental Digital Content 3, <http://links.lww.com/CJP/A227> and Figure, Supplemental Digital Content 9, <http://links.lww.com/CJP/A233>). Multiple-session in vivo exposure-based therapy was superior to single session exposure for the reduction of specific fear measured posttreatment ( $n = 93$ ; SMD:  $-0.66$  [ $-1.08, -0.24$ ]) but not at 1-year follow-up ( $n = 83$ ; SMD:  $-0.37$  [ $-0.87, 0.13$ ]). Data for the following important outcomes measured at 2 time-points (posttreatment, 1-year follow-up) are presented in the supplemental digital content (Table, Supplemental Digital Content 3, <http://links.lww.com/CJP/A227> and Figure, Supplemental Digital Content 9, <http://links.lww.com/CJP/A233>): general fear, compliance (using a BAT), and fainting. Compliance with a voluntary blood

donation or voluntary dental injection over the 12-month follow-up period is also summarized.

### Should Imaginal Exposure-based Therapy be Used for Children 7 Years and Above With High Levels of Needle Fear?

No trials were identified that studied children with a fear of needles or a related phobia. Thus, trials of other specific phobias were sought. Two trials with 41 children aged 7 to 17 years with phobias of spiders or darkness (diagnosed according to the DSM-III-R<sup>134</sup>) were included in the analysis.<sup>46,50</sup> In 1 study,<sup>50</sup> children received 6 weekly 40-minute sessions of "emotive imagery" therapy during which they engaged in a variant of imaginal hierarchical exposure in which the child was supported by his or her favorite superhero; the comparator was a waitlist control group. Of note, although the authors describe their intervention as focusing on imaginal exposure, the children were rewarded for initiating in vivo exposure between sessions.<sup>50</sup> In the other study,<sup>46</sup> children received a single 2.5-hour session of eye-movement desensitization and reprocessing therapy that included imaginal exposure combined with rapid horizontal eye movements and cognitive restructuring; the comparison group was considered a placebo group by the authors but consisted of 2.5 hours of computer-delivered exposure to the feared stimuli ranging in degree of realism (eg, cartoon-like spiders vs. ones that appeared more real). Imaginal exposure-based therapy led to a reduction in specific fear posttreatment (both trials;  $n = 41$ ; SMD:  $-0.88$  [ $-1.7, -0.05$ ]) and at 3-month follow-up (1 trial<sup>50</sup>;  $n = 24$ ; SMD:  $-0.89$  [ $-1.73, -0.04$ ]) (Table, Supplemental Digital Content 4, <http://links.lww.com/CJP/A228> and Figure, Supplemental Digital Content 10, <http://links.lww.com/CJP/A234>). Data for the following important outcomes measured at 2 time-points (posttreatment, 3-month follow-up) are presented in the supplemental digital content (Table, Supplemental Digital Content 4, <http://links.lww.com/CJP/A228> and Figure, Supplemental Digital Content 10, <http://links.lww.com/CJP/A234>): general fear, distress (parent-rated), and compliance (using a BAT).

### Should Non In Vivo Exposure-based Therapy be Used for Adults With High Levels of Needle Fear?

Two studies of adults with high levels of fear were included in this analysis.<sup>51,52</sup> One study<sup>51</sup> included 84 otherwise healthy adults who were highly fearful and avoidant of dental injections and needles (assessed by 2 questionnaires). The other trial<sup>52</sup> included 30 adults with multiple sclerosis who were afraid of injections and unable to perform necessary self-injections of their medication for at least 3 months; 12 of the 30 participants met diagnostic criteria for blood-injection-injury phobia according to the DSM-IV.<sup>135</sup> In Heaton et al<sup>51</sup> participants received computer-delivered exposure through a specialized program designed to be completed in 1 to 3, 45-minute sessions; the content of the program included relaxation training, cognitive distraction, positive coping strategies, and hierarchical exposure with modeling. The comparison group received an educational pamphlet.<sup>51</sup> In Mohr et al,<sup>52</sup> participants engaged in 6 weekly sessions (length of each session was not reported) involving psychoeducation, progressive muscle relaxation, hierarchical imaginal exposure and relaxation, cognitive restructuring, and in vivo injection attempts in the fourth and fifth sessions. The



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

References	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
<b>Should in vivo exposure-based therapy be used for children ≥ 7 y with high levels of needle fear?</b>								
Flatt 2010 <sup>40</sup>	NA	NA	NA	NA	NA	NA	NA	NA
Leutgeb 2012 <sup>45</sup>	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Muris 1998 (1) <sup>46</sup>	Unclear	Unclear	No	No	Yes	Yes	Unclear*	High
Ollendick 2009 <sup>41</sup>	Yes	Unclear	No	No	Yes	Yes	No†	High
Öst 2001 (1, 2) <sup>42</sup>	Unclear	Unclear	No	No	Yes	Yes	Yes	High
<b>Should in vivo exposure-based therapy be used for adults with high levels of needle fear?</b>								
Öst 1991 (1) <sup>47</sup>	Unclear	Unclear	No	No	Yes	Yes	Yes	High
<b>Should multiple-session in vivo exposure-based therapy be used (rather than single session) for children ≥ 7 y and adults with high levels of needle fear?</b>								
Öst 1992 <sup>48</sup>	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Vika 2009 <sup>49</sup>	Yes	Unclear	No	No	Yes	Yes	Yes	High
<b>Should non in vivo (imaginal) exposure-based therapy be used for children ≥ 7 y with high levels of needle fear?</b>								
Cornwall 1996 <sup>50</sup>	Unclear	Unclear	No	No	Unclear	Yes	Yes	High
Muris 1998 (2) <sup>46</sup>	Unclear	Unclear	No	No	Yes	Yes	Unclear*	High
<b>Should non in vivo exposure-based therapy be used for adults with high levels of needle fear?</b>								
Heaton 2013 <sup>51</sup>	Yes	Yes	No	No	Unclear	Yes‡	Yes	High
Mohr 2005 <sup>52</sup>	NA	NA	NA	NA	NA	NA	NA	NA
<b>Should applied tension (exposure and muscle tension) be used for children ≥ 7 y and adults with high levels of needle fear and fainting?</b>								
Öst 1991 (2) <sup>47</sup>	Unclear	Unclear	No	Unclear	Yes	Yes	Yes	High

\*Different therapists were used for the various groups.

†Outcome data are collapsed across country but there were baseline differences in the clinician-severity rating of the phobia (US > Sweden) and percentage of steps completed on the BAT (US > Sweden).

‡Heaton et al<sup>51</sup>; necessary data provided by the authors.

NA, this study was not included in the meta-analysis for critical outcomes for this question.

comparison group received 6 weeks of telephone support, including education on injection techniques and progressive muscle relaxation. Critically important outcomes were only available for Heaton et al.<sup>51</sup> Non in vivo exposure reduced specific fear (n = 68; SMD: -0.62 [-1.11, -0.14]) but not acute fear during a voluntary injection (n = 17; SMD: 0.18 [-0.87, 1.23]) (Table, Supplemental Digital Content 5, <http://links.lww.com/CJP/A229> and Figure, Supplemental Digital Content 11, <http://links.lww.com/CJP/A235>). The supplemental digital content (Table, Supplemental Digital Content 5, <http://links.lww.com/CJP/A229> and Figure, Supplemental Digital Content 11, <http://links.lww.com/CJP/A235>) contains data for the important outcome of compliance measured through voluntary dental injection or self-injection of medication.

**Should Applied Tension (Exposure and Muscle Tension) be Used for Children 7 Years and Above and Adults With High Levels of Needle Fear and Fainting?**

One trial with adult participants diagnosed with blood-injection-injury phobia (excluding those with only an injection phobia) according to the DSM-III-R<sup>134</sup> was included in this analysis.<sup>47</sup> Participants received 5 weekly 45 minutes to 1 hour sessions of applied tension (muscle tension + exposure); treatment included outlining the rationale for the technique, practicing muscle tension without and then with (hierarchical) exposure to feared stimuli.<sup>47</sup> The comparison group received 5 weekly 45 minutes to 1 hour sessions of in vivo exposure. Thus, this analysis compared 2 active treatments. Applied tension showed benefit on the critical outcome of fainting both

posttreatment (n = 20; SMD: -1.16 [-2.12, -0.19]) and at 1-year follow-up (n = 20; SMD: -0.97 [-1.91, -0.03]) (Table, Supplemental Digital Content 6, <http://links.lww.com/CJP/A230> and Figure, Supplemental Digital Content 12, <http://links.lww.com/CJP/A236>). Data for important outcomes of specific fear, general fear, and compliance at both time-points are presented in the supplemental digital content (Table, Supplemental Digital Content 6, <http://links.lww.com/CJP/A230> and Figure, Supplemental Digital Content 12, <http://links.lww.com/CJP/A236>).

**DISCUSSION**

This systematic review and meta-analysis is the first to examine the efficacy of exposure-based interventions for the reduction of fear in individuals with high levels of needle fears or phobias across the lifespan. Consideration of this vulnerable population within the context of vaccine injections is critical given their heightened risk for fears and avoidance of medical care over their lifetime<sup>2-15,17,29,136</sup> and complements the other systematic reviews on vaccine pain management in this series.<sup>137-142</sup>

There were no trials examining interventions specific to the vaccination context (which is perhaps not surprising given that these interventions need to take place outside of this context) and limited trials of children with high levels of needle fears or phobias, requiring us to include indirect evidence from nonvaccination and non-needle contexts. To our knowledge, there has been no published systematic examination of high levels of fear with regard to different types of needle procedures. The included trials enrolled

**TABLE 4.** Summary of Results for Critically Important Outcomes

Clinical Questions	Critical Outcomes*	Benefit of Intervention†	Quality of Evidence‡
<b>Interventions for individual with high needle fear</b>			
Should in vivo exposure-based therapy be used for children $\geq 7$ y with high levels of needle fear?	Fear	Yes	Very low
Should in vivo exposure-based therapy be used for adults with high levels of needle fear?	Fear	Mixed	Very low
Should multiple-session in vivo exposure-based therapy be used (rather than single session) for children $\geq 7$ y and adults with high levels of needle fear?	Fear	Mixed	Very low
Should non in vivo (imaginal) exposure-based therapy be used for children $\geq 7$ y with high levels of needle fear?	Fear	Yes	Very low
Should non in vivo exposure-based therapy be used for adults with high levels of needle fear?	Fear	Mixed	Very low
Should applied tension (exposure and muscle tension) be used for children $\geq 7$ y and adults with high levels of needle fear and fainting?	Fainting	Yes	Very low

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

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

‡Reflects the lowest quality of evidence rating across all evaluated critical outcomes, whereby rankings range from high to moderate to low to very low.

participants with elevated fear of a particular situation, object (typically related to needles), or both and utilized interventions that exposed them to their particular fear. Findings suggest that in vivo exposure-based therapy is effective for reducing specific fear in children (7 y and above) and adults. Among adults with high levels of needle fears, there was limited efficacy found for the superiority of delivering in vivo exposure in multiple, shorter sessions (eg, 5  $\times$  1 h) as compared with 1 relatively long session (eg, 3 h). Non in vivo (imaginal, computer-based) exposure was also found to have benefit on specific fear among children and

adults. Finally, among adults, applied tension (exposure + muscle tension) was found to have additive beneficial effects on fainting, over and above exposure alone. Taken together, these findings support the use of these exposure-based interventions for reducing fear and fainting, respectively, among individuals with high levels of needle fears or phobias.

Interestingly, in comparison with single sessions, multiple sessions of in vivo exposure were only more efficacious for reducing specific fear immediately posttreatment but not at 1-year follow-up; these results then provide only limited support for the efficacy of a longer mode of delivery.<sup>48,49</sup> Moreover, all of the trials of in vivo exposure in children, which were found to be efficacious for reducing specific fear, were single session.<sup>40–42,45,46</sup> Unlike multiple sessions that are typically an hour in length and spread out over several weeks, single sessions often involve several hours (eg, 2.5 to 4 h; Öst's traditional 1 session treatment is typically maximized to 3 h<sup>28</sup>) of exposure treatment. This results in the provision of a higher "dose" of treatment at one point in time. It is important to note that even in the single session approach, exposure still progresses in a hierarchical manner. Although there may be individual differences in terms of preferences, readiness, and tolerance for high versus low doses of this treatment, these findings suggest that effective treatment of high needle fears or phobias may need not be time intensive (ie, taking several weeks or even months); in fact, 1 session approaches for the treatment of a variety of specific phobias have increased in popularity over time.<sup>143–145</sup> Beyond relative efficiency and feasibility, the utility of 1 session treatment of high levels of needle fear could be particularly high in preparing a fearful individual for required, imminent medical treatment.

The inclusion of physical interventions (applied tension) for the management of fainting in individuals with high levels of needle fears was important given that this response is common in those with an extreme fear of blood and needles (70% and 56%, respectively<sup>29</sup>). In the vaccination context, fainting is particularly concerning given the potential for injuries as a result of falling.<sup>146–149</sup> There may be several mechanisms underlying the efficacy of applied tension, including both physiological (raising blood pressure) and psychological (interoceptive exposure leading to changes in cognitions about the uncontrollability of fainting) mechanisms. The evidence supports the additive benefit of muscle tension in addition to in vivo exposure in adults. Most impressive were the long-term effects found for fainting posttreatment and at 1-year follow-up, which speaks to the robustness of this technique. Although the current findings were based on the single trial that answered the clinical question, extant research also supports the use of applied tension for a reduction in fainting in the context of blood-injection-injury phobia.<sup>31,33,116,120</sup> These findings warrant replication in individuals spanning various age groups to determine whether this technique can be developmentally tailored to younger populations.

Overall, there was a striking dearth of research examining interventions for individuals with high levels of needle fears or phobias. We included children and adults with high levels of needle fear and or phobias undergoing vaccination or other needle procedures, followed by the next closest context. We included individuals with a diagnosis of blood-injection-injury phobia or another related phobia (eg, injection phobia) as well as individuals with high levels of needle fear and related functional impairment

(eg, being unable to self-inject medicine for their chronic illness management). There were limited trials of blood-injection-injury phobia in adults and no trials in children. In the absence of randomized or quasi-randomized controlled trials on individuals with high levels of needle fears or phobias, we were required to rely on trials of individuals with specific phobias that were unrelated to needles (eg, spider and darkness phobias). Although only occurring for children, this may threaten the generalizability of the current findings to needle contexts. Indeed, individuals with phobias and high levels of fear are not a homogenous group and their response to feared stimuli and intervention are invariably influenced by the specific catastrophic cognitions underlying their fears. In short, extrapolating findings from non-needle-related contexts to the vaccination context is potentially problematic. Nevertheless, this systematic review offers important, new knowledge about effective fear management in this vulnerable group that can be applied to vaccination to guide future research in this area.

Needle phobia has fallen under the diagnostic umbrella of blood-injection-injury phobia and substantial similarities between individuals with phobias of blood and phobias of injections have been documented.<sup>29</sup> Nevertheless, given the breadth of the diagnostic category, the specific focus of the fear can be quite diverse across individuals (eg, seeing injuries or mutilation vs. receiving a needle).<sup>17</sup> Thus, we were limited in our review by the field's conceptualization of the phobia. Disgust sensitivity has been implicated in certain specific phobias, including blood-injection-injury phobia.<sup>150,151</sup> Blood and injury stimuli (vs. injection) may be more likely to elicit disgust.<sup>152</sup> In fact, disgust may emerge due to fears of contamination<sup>150,151</sup>; thus, the specific focus of fear may be critical (eg, is the individual fearful of the pain, being contaminated by the needle, fainting, or something else?). Only one of the trials (focused on children with spider phobias) included in the current review measured disgust, finding that exposure reduced both fear and disgust.<sup>45</sup> It is important to note that even among people who fear needles specifically, the focus of individuals' fears may differ (eg, they may fear blood, injections, insertion of foreign substance into their bodies, and/or the medical context<sup>153</sup>). Differences in the focus of fear would be expected to influence ones' response to particular interventions.

Fears of needles can extend beyond the needle context and follow a chronic course<sup>17,29,136</sup>; therefore, longitudinal examinations that include the postintervention time period (weeks, months, and years later) are important. Unlike the other reviews in this series, many of the trials of interventions for individuals with high needle fears or phobias included long-term follow-up assessments as well as inclusion of other outcomes deemed to be important by stakeholders invested in vaccination (eg, compliance, fainting, satisfaction). This was a strength of this systematic review. Although immediate outcomes reflect the short-term efficacy of an intervention, the overall utility of an intervention is questionable if findings are not maintained over time. In vivo exposure was found to have effects on immediate posttreatment outcomes; however, less support was found for longer term outcomes (1y posttreatment). Among children, non in vivo exposure had effects on specific fear that were maintained at 3-month follow-up, and applied tension had effects on fainting that were maintained at 1-year follow-up. This suggests that while some of these interventions have lasting effects, some individuals with high levels of needle fears or phobias may require additional intervention to retain reductions of fear over longer

periods of time. The use of booster sessions in cognitive-behavioral treatments for many disorders (eg, anxiety, depression) is well known.<sup>154</sup> Booster sessions may be particularly important for individuals with a high level of needle fear who may go relatively long periods without being exposed to a needle procedure.

Pain was not included as an outcome in the included trials (due to the indirectness of the evidence) but has important implications for needle fears and should be included in future research. The relationship between needle pain and fear is likely reciprocal and should be further delineated. An exploration of the likely complex etiology of needle fears is presented elsewhere in this series.<sup>20</sup> However, most individuals with high needle fears or phobias can root their fear back to 1 traumatic needle procedure in their past.<sup>29,155,156</sup> Early vicarious and instrumental learning processes may make individuals more vulnerable to experiencing and perceiving greater pain during needle procedures.<sup>20,157</sup> Conversely, individuals whose pain is poorly managed during needle procedures are more likely to develop increasingly fearful memories of the procedure<sup>158</sup> that then places them at risk for experiencing more distress at subsequent needle procedures.<sup>159</sup> This can fuel a vicious self-perpetuating cycle of increased needle fear and pain over time.<sup>157</sup> Effective pain management may serve to help prevent needle fears from developing. In short, effective management of pain and fear may serve to reduce future fear and pain and hold promise for preventing distress and impairment (eg, noncompliance) over time. Given that concerns about pain and fear are known contributors to vaccine hesitancy,<sup>12,16</sup> effective management of both is paramount.

Consideration of the strengths and limitations of this body of work creates clear pathways for future research. High-quality RCTs of exposure-based interventions with individuals with high levels of needle fear are critically needed, for the vaccination context and otherwise. Ideally, these trials should: (1) enroll sufficient numbers of participants in narrow age ranges to adequately capture developmental differences; (2) assess and report fainting history as well as the specific focus of the needle fear (eg, pain from the needle, injection of a foreign substance) both at baseline and in response to treatment; (3) clearly report and connect the target(s) of the exposure with the focus of the needle fear; and (4) continue to gather longitudinal data as well as expanding the outcomes and follow-up time frame if possible (eg, beyond 1y) with and without booster sessions. Discussion of implementation considerations is beyond the scope of the present paper and the reader is directed to our clinical practice guideline on the management of high levels of needle fear that explores these issues in detail<sup>160</sup>; however, future research should also be conducted on various delivery methods of these interventions to enhance feasibility and uptake.

In conclusion, we applied a rigorous methodological approach to conduct the first systematic review of exposure-based interventions for the reduction of fear in individuals of all ages with high levels of needle fears or phobias. No trials specifically examined interventions implemented in the vaccination context and trials of individuals with high levels of needle fears or phobias were limited. Support was found for the efficacy of in vivo and non in vivo exposure therapy for reducing specific fear in individuals with high levels of needle fears or phobias. Multiple sessions of in vivo exposure were not clearly superior to single sessions. Applied tension was efficacious for reducing fainting in adults. These findings suggest that these interventions hold promise for reducing vaccine

injection fear in individuals who are particularly vulnerable for experiencing fear and avoidance of medical care over time.

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