Reducing Pain In Four- To Six-Month Old Infants Undergoing Immunization Using A Multi-Modal Approach

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Pharmaceutical Sciences
University of Toronto

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Abstract

**Background:** Infant immunization pain is not currently well managed despite effective strategies.

**Objective:** To determine the effectiveness of tactile stimulation when added to a combination of pain-reducing interventions in infants undergoing immunization.

**Methods:** Healthy infants aged 4-6 months undergoing immunization in primary care were randomized to tactile stimulation or usual care. All infants also received pain-relieving interventions. A validated measure of acute pain in infants, the Modified Behavioral Pain Scale (MBPS), was the primary outcome.

**Results:** Altogether, 120 infants participated. Characteristics did not differ (p > 0.05) between those allocated to tactile stimulation and usual care groups. Mean MBPS pain scores did not differ between groups: 8.2 (1.1) vs. 8.0 (1.3), respectively; p = 0.57.

**Conclusions:** Parent-led tactile stimulation did not improve pain relief in infants when added to other interventions. Parental attention could have been focused on tactile stimulation, preventing parents from performing appropriate soothing activities. Additional investigation of the effectiveness of clinician-led tactile stimulation is recommended.
Acknowledgments

This work is dedicated to the memory of my parents, Mel and Bonnie Hogan.

First and foremost, I would like to thank my supervisor Dr Anna Taddio who has provided excellent learning opportunities, knowledge and expertise, as well as guidance and support throughout my studies. I also thank my committee members Drs Rebecca Pillai Riddell and Joel Katz for their advice and encouragement during this research.

I thank the staff at Women’s College Hospital Family Practice Health Centre and the parents and infants who participated in this study.

I want to thank the undergraduate students who helped the project by coding the primary outcome (MBPS): Angela Girgis, Linda Wang, Sandra Gerges. I thank them and the other undergraduate students for entering data and checking data accuracy: Jinju Yoon and Michelle Tan. I want to especially thank Erwin Darra for initial videotaping of procedures, transferring videotapes to DVDs, coding cry time and MAISD, and for serving as the technology consultant for all things audiovisual.

I would like to acknowledge sources of financial support I received during my studies: a Canadian Institutes of Health Research Master’s Scholarship and a Pain In Child Health Research Training Consortium Award.

Lastly I would like to thank my family and friends who provided encouragement and distraction when needed, who listened to, sometimes counselled and always supported me during my studies.
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Chapter 1

1 Introduction

1.1 Statement of the problem

1.1.1 Burden of pain

Immunization is the most common painful medical procedure in healthy infants. In Ontario, infants undergo at least eight separate immunizations in their first year of life. Therefore, routine immunization causes a significant burden of pain and distress for otherwise healthy infants and their families.

1.1.2 Treatment options

Several modalities to reduce pain in infants during immunization are currently available, including pharmacological, behavioural and injection techniques. The following options are recommended in an evidence-based clinical practice guideline:

1. Oral sucrose is effective, and is recommended for infants up to approximately 12 months of age.
2. A fast injection technique without aspiration is less painful than the traditional slow insertion, injection and aspiration technique.
3. When diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenzae type B (DTaP-IPV-Hib) and pneumococcal conjugate vaccine (PCV) immunizations are given at a single visit, giving DTaP-IPV-Hib (the less painful injection) first causes less overall pain.
4. Physical behaviours such as holding the infant are advocated in practice guidelines and the upright position has been found to be associated with less fear and decreased crying after immunization compared to the supine position.
To determine the effectiveness of tactile stimulation in reducing immunization injection pain in infants.

1.2.2 Primary research question

In healthy four- to six-month old infants undergoing routine DTaP-IPV-Hib and PCV immunization while receiving a combination of proven analgesic interventions (least painful
injection technique, holding by parent, and oral sucrose solution), does the addition of rubbing near the injection site reduce overall pain (mean of both injections) compared to no rubbing as measured by a validated measure, the Modified Behavioral Pain Scale (MBPS)?

1.2.3 Secondary questions

1. In healthy four-to six-month old infants undergoing routine DTaP-IPV-Hib and PCV immunization, does rubbing reduce pain compared to no rubbing for each vaccine, as measured by MBPS?

2. In healthy four-to six-month old infants undergoing routine DTaP-IPV-Hib and PCV immunization, does rubbing reduce pain compared to no rubbing as measured by VAS and cry duration for each vaccine and both together?

3. Do parents prefer one of the two treatments?

1.3 Research hypotheses and rationale

1.3.1 Hypotheses

1. Tactile stimulation will be effective in reducing overall pain response during immunization with DTaP-IPV-Hib and PCV.

2. Tactile stimulation will be effective in reducing pain response during each of the two immunizations with DTaP-IPV-Hib and PCV.

1.3.2 Hypotheses rationale

Previous studies of tactile stimulation in adults and children being immunized have shown that applying pressure to the site prior to injection or rubbing adjacent to the site reduces injection pain. One study in neonates undergoing heel lance showed that massaging the ipsilateral leg just before the procedure reduced the pain response. However, there are no trials of tactile stimulation for immunization injections in infants. Importantly, none has tested tactile stimulation when added to a combination of proven pain reducing measures or had parents deliver the intervention.
1.4 Literature review

1.4.1 The nociceptive system and gate theory of pain

Massage is a type of tactile stimulation that involves the “manipulation of tissues (as by rubbing, kneading, or tapping) with the hand or an instrument for therapeutic purposes.”\(^\text{22}\) The benefits of ongoing massage therapy may be explained by more than one mechanism of action. Serotonin is released, possibly resulting in improved modulation of pain\(^\text{23}\) and improvement in sleep deficits may occur which may decrease the production of substance P.\(^\text{24}\)

Tactile stimulation such as rubbing the skin for several seconds prior to and during an injection is distinct from massage therapy which occurs for many minutes to hours. The well-established gate theory of pain,\(^\text{25, 26}\) provides the best explanation for the immediate effects of rubbing therapy and its potential for alteration of pain signal transmission associated with immunization.

Nerves in the skin are typically composed of primary sensory afferent neurons, motor neurons and sympathetic postganglionic neurons. The primary sensory afferent neurons are responsible for the sensation of pain and touch. They include A-delta neurons, responsible for the sharp pain felt at the time of needle insertion, C-neurons, responsible for dull, aching, longer lasting pain after an injury, and A-beta neurons, activated by touch rather than pain. The largest, A-beta neurons, have the fastest conduction velocity, at 50 metres per second. This compares to A-delta neurons at 15 metres per second and the smallest, C fibres, at 1 meter per second.\(^\text{27}\) In the dorsal horn of the spinal cord, these afferent neurons synapse with spinal cord transmission cells and signals continue to the brain where they are perceived as pain. The process is “gated” at the spinal cord transmission cell by input from both large and small fibre neurons. When input from large fibre neurons such as A-beta is high, the “gate” is closed (transmission is inhibited) and when input from smaller fibre neurons such as A-delta and C is high, the “gate” is opened (transmission is facilitated) and spinal neurons carry the impulses to the brain via the spinothalamic tract.

If A-beta neurons are stimulated at the same time as A-delta and C neurons, the signals from A-beta fibres will reach the synapse first and may inhibit or close the gate to pain signals.\(^\text{25, 26}\)

It is postulated that light rubbing in the area close to the site of an immunization injection will activate A-beta neurons which will close the gate. Transmission of pain signals arising from the
injection will, therefore, be inhibited at the level of the spinal cord. The proximity of rubbing and injection site would be expected to facilitate gating for the appropriate spinal neurons.

An early study of experimental pain demonstrated the effect of tactile stimulation on pain reduction. Participants were given increasing levels of electrical shocks on their forearm via an electrode, starting with an intensity they could not feel. The subject indicated when he could first feel it (threshold), when it became uncomfortable, when it became painful and when he could no longer tolerate it (tolerance). A blood pressure cuff with a comb-like stimulus inside was attached to the subject’s forearm distal to the electrode to deliver a reproducible method of tactile stimulation that was considered to be similar to light touch. The tactile stimulation began 0.75 seconds before the electrical stimulation and continued for the duration of the shock (1 second). Each subject participated with the blood pressure cuff on the same side as the shock, on the opposite side of the shock and without the cuff (presentation order varied among subjects). Threshold shock, which is not painful, was the same in all groups. The group receiving ipsilateral tactile stimulation of the forearm was able to tolerate a higher intensity of current before judging it to be uncomfortable, painful or intolerable compared to contralateral or no tactile stimulation (p < 0.05 for each judgement). Stimulation on the same arm (but not the opposite arm) increased pain tolerance; this makes it unlikely to be only distraction, or “masking” (feeling one sensation rather than the other) from the stimulus, which should occur whether it is administered on the same or opposite site. Tactile stimulation on the ipsilateral arm did not change the point at which electrical stimulation was first felt, which is generally not perceived as a painful, but did increase tolerance at the points considered to have negative sensation; simple distraction or “masking” should also have an impact on the threshold. This experiment helps clarify that tactile stimulation is more than simple distraction or “masking” and the findings are consistent with the gate theory of pain.

1.4.2 Studies of tactile stimulation to reduce pain

A number of studies have examined different types of tactile stimulation given at the time of injection or needle insertion compared to usual care and found a reduction of pain in groups receiving the intervention (see Table 1).
In adults, two studies tested the effect of pressure applied to the injection site prior to receiving an immunization injection. In one study, 93 adults receiving immune globulin were randomized to receive 10 seconds of pressure at the injection site, or no pressure prior to receiving the injection. Pain was measured by a 10 cm visual analog scale (VAS). The group receiving pressure rated their pain as 1.36 cm compared to 2.15 cm in the control group (p = 0.03). In another study, 74 adults who were receiving injections for hepatitis A and B received one injection with pressure applied before the injection, and the other without pressure. Pain was measured by a 10 point Pain Intensity Verbal Rating Scale (Cantonese). The mean pain score for injections with prior application of pressure was 1.77 versus 2.86 for usual care (p < 0.001).

Two other studies have used tactile stimulation to reduce pain from intramuscular or subcutaneous injections in adults. Sixty-four adults received two intramuscular injections of penicillin ± procaine in the buttocks. For one injection, they received massage for 1 minute and pressure at an acupressure point by a nurse who had received training in this technique. The other injection was done without massage or pressure. The order of injections and side of injection were randomized. Pain was measured by self-report of a number between 0 and 10. The mean pain score was 3 for the acupressure injection and 5 for the no-acupressure injection. The Wilcoxon test found pain perception to be 2.5 points lower in acupressure group (p < 0.001).

A study of 212 adults receiving ceftriaxone intramuscularly and enoxaparin subcutaneously employed the use of a plastic disk (54 mm x 40 mm) of blunt pins (9 per cm²) with a hole in the middle. The disk was placed on the skin and the injection was done through the hole in the centre. Patients received ceftriaxone 2 g intramuscularly in the gluteus region and enoxaparin subcutaneously in the deltoid region. Patients were allocated to treatment or control groups based on chart numbers. Pain was measured using a 10 point VAS. Pain was lower in the treatment group compared to control (intramuscular: 1.90 versus 5.16, p < 0.001; subcutaneous 0.32 versus 2.61, p < 0.001).

A study in adults had also investigated tactile stimulation for pain reduction from insertion of needles into muscle for electromyography (EMG). Finger-slapping of the skin beside a needle insertion was studied in 77 patients undergoing EMG investigations of their bilateral gastrocnemius or anterior tibial muscles. Patients underwent two needle insertions for the EMG investigation. For the pain study, participants received simultaneous finger-slapping of the
skin beside the needle at the same time as insertion for one needle and no finger-slapping for the second needle. Participants rated pain intensity after each needle insertion using a 10 cm VAS. The order of slapping with needle insertion was randomized. Pain was rated at 0.71 cm when accompanied by finger-slapping and 1.78 cm when no finger-slapping was used ($F = 32.21$, $p < 0.001$).

Two studies have studied tactile stimulation in preterm babies as a method to reduce pain associated with heel stick. In a very small study of 8 infants (32 - 34 weeks), stroking the opposite foot was found to result in a smaller decrease in oxygen levels (suggestive of less pain) than standard therapy although no statistical comparisons were performed. In the more recent study of 23 pre-term infants from one to seven days post birth, a two minute massage of the ipsilateral leg prior to heel stick was compared to no massage. The results were compared with a second heel stick two to seven days later. The order of massage (first or second heel stick) was randomized. The rater was blinded to group assignment. Neonatal Infant Pain Scale (NIPS) scores were lower for infants when they had received prior massage compared to the no-massage injection (1.5 versus 3.5, $p < 0.001$).

A study of 105 children aged 4 to 6 years undergoing immunization with diphtheria-tetanus-pertussis (DTP) were randomized to one of three treatments: light stroking of the skin near the injection site, bubble blowing by the child, or standard care. Pain was measured with the 10 point self-report Oucher scale. No statistical difference was found between light stroking and bubble blowing, although numerically less pain was reported in the light stroking group (1.89 versus 2.00). Both treatments together resulted in less pain than the control group (2.89, $p = 0.013$). The authors of this study noted that many children in the bubble blowing group stopped to focus on the injection despite coaching to continue with the bubbles. Since distraction requires the child be engaged, the group receiving light touch many have been at an advantage because the intervention did not require the child to attend to the activity.

One additional concern about the available literature is the role of blinding in the studies. In all but one infant study, pain was rated by the individual who received tactile stimulation; because participants were aware of the intervention, it is possible that their responses were biased based on expectation of the effectiveness of the intervention. In addition, for same-day cross-over studies, order of administration was not disclosed and this has been shown to have an effect on
pain experience. The two other adult studies and the study in children aged 4 - 6 years were not truly randomized and allocation to treatment groups was not concealed. These factors have been shown to be associated with larger treatment effect than when allocation is adequately concealed. In addition, the findings from studies in pre-term infants may not be directly applicable to older infants due to rapidly developing neurological systems and change in the way pain is expressed over this time.

While there is some evidence for tactile stimulation, and its mechanism of action is supported by the gate theory of pain, the current evidence for tactile stimulation for pain reduction in infants is limited. Moreover, only one of these paediatric studies was for injection pain and was studied in 4 to 6 year-old children. The current guideline for management of immunization pain recommends tactile stimulation for age four and up since no evidence exists for younger ages. It is an intervention that could be easily incorporated into practice with limited training and no cost to the health system or individuals. A study was needed to determine effectiveness in ages younger than four years.
**Table 1: Randomized controlled trials of tactile stimulation**

<table>
<thead>
<tr>
<th>Population</th>
<th>Procedure</th>
<th>Intervention/Comparison</th>
<th>Design</th>
<th>Pain measurement tool*</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93 adults&lt;sup&gt;18&lt;/sup&gt;</td>
<td>immune globulin injection in buttocks</td>
<td>10 seconds of thumb pressure prior to injection versus no pressure.</td>
<td>Pseudo-randomized †</td>
<td>VAS (10 mm)</td>
<td>Less pain in the intervention group (1.36 cm versus 2.15 cm, p=0.03)</td>
</tr>
<tr>
<td>74 university students&lt;sup&gt;19&lt;/sup&gt;</td>
<td>IM hepatitis A and B vaccines in arm</td>
<td>10 seconds of thumb pressure prior to injection versus no pressure; pressure-sensing device was used.</td>
<td>Randomized cross-over at same visit</td>
<td>Pain Intensity Verbal Rating Scale (Cantonese) (10 points)</td>
<td>Less pain in the intervention group (1.77 versus 2.86 p&lt;0.001).</td>
</tr>
<tr>
<td>64 adults&lt;sup&gt;20&lt;/sup&gt;</td>
<td>two IM injections of penicillin ± procaine in the buttocks</td>
<td>1 minute rubbing and pressure at an acupressure point versus no rubbing or pressure.</td>
<td>Randomized cross-over</td>
<td>10 point scale</td>
<td>2.5 points lower in acupressure group (p&lt;0.000).</td>
</tr>
<tr>
<td>212 adults in hospital for orthopaedic surgery&lt;sup&gt;21&lt;/sup&gt;</td>
<td>ceftriaxone 2 g IM in buttocks, enoxaparin SC in arm</td>
<td>Application of plastic disk (54 mm x 40 mm) of blunt pins (9 per cm&lt;sup&gt;2&lt;/sup&gt;) with a hole in the middle for injection to site at time of injection or placebo disk (no pins).</td>
<td>Pseudo-randomized ‡</td>
<td>VAS (10 point)</td>
<td>Less pain reported in groups using disk with pins. IM: 1.90 versus 5.16, p&lt;0.001; SC: 0.32 versus 2.61, p&lt;0.001.</td>
</tr>
<tr>
<td>77 adults&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2 needle insertions for electromyographic test of bilateral gastrocnemius or anterior tibial muscle</td>
<td>Simultaneous finger-slapping of the skin beside a needle insertion versus no finger slapping.</td>
<td>Randomized cross-over at same visit</td>
<td>VAS (10 cm)</td>
<td>0.71 cm for intervention versus 1.78 cm (F = 32.21, p &lt; 0.001).</td>
</tr>
</tbody>
</table>

* For all tools, higher numbers represent more pain; VAS=visual analog scale (a horizontal or vertical line which raters mark to represent amount of pain); TcPO<sub>2</sub>: transcutaneous PO<sub>2</sub>; NIPS: neonatal infant pain scale; DTP: diphtheria-tetanus-pertussis; NICU: neonatal intensive care unit.

† Alternate assignment to groups after initial coin toss.

‡ Odd numbered charts were assigned to one group, even numbered charts were assigned to the other group.
### Population | Procedure | Intervention/Comparison | Design | Pain measurement tool | Outcome*
--- | --- | --- | --- | --- | ---
**Paediatrics**
8 preterm infants (32-34 weeks; 2-5 days old) in NICU[^32] | Heel stick | Simultaneous stroking of opposite foot versus no stroking. | Randomized cross-over (time between heel sticks not reported) | Heart rate, blood pressure and TcPO$_2$ | No statistical analysis done. Heart rate and blood pressure increased by a similar amount; TcPO$_2$ decreased to a greater degree in the group receiving the intervention (-8.9% from baseline versus -4.3% at 35 seconds, -11.1% from baseline versus -5.6% at 65 seconds). |
23 preterm infants (28-35 weeks; 1-7 days old) in NICU[^21] | Heel stick | 2 minute rubbing of ipsilateral leg prior to heel stick versus no rubbing. | Blinded, randomized, cross-over (2-7 days apart) | NIPS (10 points) | Less pain with rubbing: 1.5 versus 3.5, p<0.001. |
105 children aged 4-6 years from school based program[^20] | DTP vaccine IM in leg | Light stroking of the skin near the injection site prior to and during injection, bubble blowing by the child, or standard care. | Pseudo-randomized** | Self-report Oucher scale (10 points) | Both treatments (1.89 and 2.00) together resulted in less pain than control (2.89, p=0.013). No statistical difference between light stroking and bubble blowing (1.89 versus 2.00). |

* For all tools, higher numbers represent more pain; VAS=visual analog scale (a horizontal or vertical line which raters mark to represent amount of pain); TcPO$_2$: transcutaneous PO$_2$; NIPS: neonatal infant pain scale; DTP: diphtheria-tetanus-pertussis; NICU: neonatal intensive care unit.  
** Order of first three participants was determined by drawing lots and the remainder followed the same order.

### 1.4.3 Consequences of untreated pain

Untreated pain has consequences for infants. In the short term, untreated pain causes behavioural changes (crying, facial grimacing, thrashing or withdrawing limbs) increases in heart rate and blood pressure as well as oxygen desaturation.[^36] In the long term, it can lead to the development of pre-procedural anxiety due to conditioning, and needle fears, including phobia. Needle fears lead to avoidance of medical treatment later in life.[^36-38] Therefore, it is important to effectively manage pain in infants.
Untreated pain in children also causes distress for parents and healthcare workers. A survey of parents found they preferred more injections (3 or 4) for their child at a single visit (rather than giving fewer at two visits) in order to decrease the number of visits for immunizations. Physicians in the same survey expressed increasing concern with an increasing number of injections at a single visit. Physicians and parents have cited pain as a reason for not adhering to recommended immunization schedules, not surprising since a study of caregivers in an emergency department found an increase in anxiety and heart rate while watching their child undergoing a venipuncture.

Early painful experiences have been associated with larger pain response later in infancy. For example, infants who were circumcised as neonates had larger behavioural pain scores and cried longer than non-circumcised infants when immunized at a later date. Therefore, factors such as birth experience (Caesarean delivery, use of forceps or vacuum), circumcision and illness requiring hospitalization or hospital stays of at least a week at birth (which may include repeated skin-breaking procedures) were recorded during baseline data collection to ensure no differences between groups.

1.4.4 Current pain management for immunization

Despite availability of multiple pain-relieving options, immunization pain is not routinely managed in an effective manner. Topical anaesthetics are administered to 0% of infants undergoing immunization (and 1% of children). Physicians cited extra cost and time as barriers to using topical anaesthetics. Parents, on the other hand, said they were unfamiliar with the drugs, and would likely use them if their physician recommended them. Other possible reasons for inadequate pain management include parent or clinician lack of knowledge about the efficacy and safety of therapies, preparation to administer, and lack of concern about pain associated with immunization.

This study aimed to incorporate proven non-pharmacologic pain relieving strategies and to evaluate the additional value of tactile stimulation. This intervention was ideal as it could be implemented in any setting without disruption, planning, extra time or cost.
1.4.5 Choice of Modified Behavioral Pain Scale (MBPS)

Pain is a subjective experience and the gold standard for measurement is patient self-report. Therefore, in pre-verbal children, pain measurement is problematic. While some physiological changes have been used to assess pain (e.g. heart rate, blood pressure, oxygen saturation) the changes are not specific to pain and are difficult to interpret.\textsuperscript{46} The MBPS is a behavioural measure that examines facial expression, cry and body movement by assigning each a score to determine overall pain and was used in this study to assess the primary outcome. A copy of the scale can be found in Appendix A. The MBPS scale has been used in several previous trials of pain and distress assessment in infants,\textsuperscript{8,13-16} and is validated for use in this population for immunization pain.\textsuperscript{47} It was adapted from the Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS), a well-established tool in older children.

The MBPS has demonstrated good concurrent validity with observer VAS (0.68, p < 0.001) and paediatrician VAS (0.74, p < 0.001). Construct validity was demonstrated by significantly lower pre-injection than post-injection scores (1.9 versus 7.3, p < 0.01) and by significantly lower scores in the group treated with lidocaine-prilocaine compared to placebo (6.8 versus 8, p < 0.01). Inter-rater agreement among five raters was 0.95, p < 0.001 using intraclass correlation and test-retest reliability was also high (0.95, p < 0.001). It demonstrated clinical utility and was more feasible than two other scales for acute pain in infants (NIPS, Face Legs Activity Cry Consolability [FLACC]) since it was preferred by raters and the tool took less time to use.\textsuperscript{48} It is also recommended in the immunization pain management guideline.\textsuperscript{4}

1.5 Summary and strategy

1.5.1 Summary

Infants experience at least eight separate immunization injections in their first year of life. Parents want to mitigate immunization pain. An effective method of reducing pain from immunization in this age group which can be easily incorporated into usual practice is needed. Rubbing of the area near the injection site is a cost-neutral, feasible intervention to reduce immunization pain that has been shown to be effective in children aged 4 and above, but had not
yet been evaluated in infants undergoing immunization. Therefore, a study was warranted to assess its effectiveness in this population.

1.5.2 Strategy

An analgesic approach that is feasible from a time requirement, and that reliably minimizes pain to low levels is needed. We proposed a study that would determine the effectiveness of rubbing the thigh near the injection site to reduce pain compared to no rubbing when added to other proven pain reducing interventions.

The proposed study was a randomized, single-blind, parallel, two group trial of tactile stimulation or no tactile stimulation in four- to six-month old infants undergoing routine immunization at an outpatient primary care clinic in a metropolitan centre. The site where the study took place had already begun to introduce pain relieving strategies into their practice and wanted to continue this practice, so the proposed study added tactile stimulation to a combination of pain reducing strategies.

All infants benefited from other proven analgesic interventions being used in the study site including:

- Least painful injection technique without aspiration
- Holding by a parent
- Oral sucrose solution

In addition, parents in both groups were encouraged to try to distract their infants because it has been associated with less distress;\(^{49}\) however, randomized trials in infants\(^{50,51}\) and older children\(^{52}\) have not found it to be effective in reducing pain, except observer-rated distress, perhaps because parents are unable to engage their infant. Tactile stimulation is a behavioural intervention that does not require engagement of the infant and so might be more successful.

Infants had pain assessed while receiving their routine DTaP-IPV-Hib and PCV vaccines, as per the Ontario immunization schedule in place during this study.\(^2\)
1.5.3 Immunization schedule

In Ontario at the time of the study, infants received DTaP-IPV-Hib and PCV at 2, 4 and 6 months of age. Different injections are given at one year and beyond. A study investigating immunization pain must ensure the same vaccines are used to minimize the variability in pain response due to the injected liquid. Therefore, this study was necessarily limited to a small age range. Infants would participate once only in the study so it was felt that allowing for two opportunities to reach them (at 4 and 6 months) was sufficient and pain behaviours were likely to be more similar in the narrower range of 4 - 6 months than if 2 - 6 months was employed. Infant visits rarely occur precisely on 4 and 6 month “birthdays;” therefore, an upper age range of 7.5 months was used to allow for infants who came later than recommended.
Chapter 2

2 Methods

2.1 Study design and setting

A single blind, randomized controlled trial was conducted at Women’s College Hospital Family Practice Health Centre, an outpatient, multi-team family practice clinic.

2.2 Blinding

Study personnel: Neither the candidate (who acted as research assistant and study coordinator) nor the clinician administering the injection could be blinded to the use of tactile stimulation as they were present for the manipulation and coordinated the injection with parent rubbing. A sham procedure of light touch could not be employed as a means to blind study personnel since it could also have a therapeutic effect.

Parents: Parents were told by the candidate that the study was evaluating several non-drug techniques to decrease pain and they were blinded to the study hypothesis. Every parent was given a one-page information sheet with instructions on minimizing their child’s pain and distress (Appendix B). The sheet contained information about parent behaviours and positioning of the infant. Parents in the no-rubbing (control) group (half of the participants) were told they were assigned to a pain-minimizing injection technique that includes sucrose analgesia, parent holding and behaviours that reduce stress (which was the same in the group receiving the rubbing intervention). In the rubbing group (half of the participants), information on the use of rubbing was added to the information sheet. Thus, parents were blinded to the intervention that was being assessed. They were debriefed by the candidate about the exact differences between study groups after the study. In this way, the influence of bias on the study results (i.e. parent VAS scores, parent acceptability and feasibility survey) was minimized.

Pain assessor(s): A videorecording of the procedure was used for scoring pain. Videotapes were scored by a coder blinded to the study hypothesis. A standardized approach was used for procedures. Although the coder may have been able to see whether or not rubbing was being
performed, bias was reduced because she was initially not aware what intervention was being investigated and was not aware of the study hypothesis.

2.3 Ethics

The study was approved by the research ethics boards of Women’s College Hospital (protocol 2009-0019) and the University of Toronto (protocol 24214). The study was registered with ClinicalTrials.gov (NCT00954499). The candidate prepared both ethics submissions and created the ClinicalTrials.gov record.

2.3.1 Ethical aspects and participant consent

Written, informed consent was obtained from parents by the candidate. Obtaining consent in a study of infants and children is unique due to the inability of the participant to provide consent. The study adhered to guidelines for the ethical conduct of studies of analgesia in children.\textsuperscript{53-55} Parents received detailed information about the study and their freedom to withdraw at any time without impact on the care of their child (see Appendix C for a copy of the consent form). After the procedure, they were told about the specific interventions under evaluation.

2.4 Study participants

Infants were identified by the lead nurse at the site (JP), who reviewed the patient appointment lists for infants attending their four or six month routine appointments. Appropriate team nurses (who administer vaccines in this practice) were alerted, either by the lead nurse or the candidate. The nurse pre-screened infants for known impaired neurological development, history of seizure and parental language. Remaining parents and their infants were approached by their clinician at the time of the appointment for routine immunization. The candidate (study coordinator) screened potential participants for eligibility by reviewing inclusion and exclusion criteria. If all criteria were met, the candidate described the study to the eligible parents and obtained consent. The candidate subsequently coordinated the study and collected the study data.
2.4.1 Inclusion criteria

All infants aged four to six months who were receiving routine DTaP-IPV-Hib and PCV vaccines at a primary care office in Toronto were eligible for participation. Use of acetaminophen and/or ibuprofen was not an exclusion criterion and was noted. We are not aware of any studies that evaluate these oral analgesics for reduction of the immediate pain from injection. 56

2.4.2 Exclusion criteria

Infants with any of the following were excluded:

- impaired neurological development
- history of seizure
- use of topical local anaesthetics at the injection site
- use of sedatives or narcotics in the preceding 24 hours
- fever or illness that would prevent administration of the vaccine
- parent was unable to use the assessment tools in the study
- parent did not speak English to their infant
- prior participation in this trial

No attempt was made to systematically track numbers of parent-infant dyads who were excluded due to any of these factors.
2.5 Randomization

An individual not directly associated with the execution of the trial (another graduate student) created a randomization code in blocks of four to eight, using a computer random number generator and created consecutively numbered opaque envelopes containing treatment allocation. The randomization code could not be accessed by study personnel. At the time of enrolment into the study, participants were assigned to the next available study number. The candidate opened the next envelope (and revealed allocation) after consent was obtained and before immunization was given. There was no opportunity for study personnel to know in advance what group the next participant would be assigned to.

2.6 Treatment intervention

Group 1 infants were rubbed on the ipsilateral thigh by the parent for 15 seconds prior to the immunization injection, during, and for a 15 seconds following immunization. Prior to the procedure, the candidate coached the parent to rub the infant’s leg just above the knee, approximately 6-8 cm from the injection site. The location on the leg was chosen for practical reasons and because it was close to the injection site.

Group 2 did not receive tactile stimulation on the thigh.

Prior to the procedure, the candidate coached parents in both groups to provide verbal distraction to their infant.

2.6.1 Procedures for all groups

1. All infants were videotaped for 1 minute before sucrose administration and for 2 minutes after the second injection

2. The clinician administered sucrose solution (2 mL, 24% solution) by oral syringe starting approximately two minutes prior to the first injection, and completing 30 seconds before the first injection.
3. Infants were held by a parent according to standard practice at the clinic: the infant sat on the parent’s lap facing outward. The infant’s lower legs were prevented from moving by trapping them between the parent’s legs. The parent also held the infant’s arms still with their hands.

4. The DTaP-IPV-Hib vaccine was administered before PCV using a fast injection technique without aspiration.

5. One minute following the first injection, or after the infant settled (whichever was longer), the second injection (PCV) was given by the same technique in the opposite leg.

6. A 25 gauge needle 25 mm (1”) in length was used for all injections.

7. No restriction on the use of acetaminophen or ibuprofen was required; however, its use was documented for later analysis.

2.6.2 Tactile stimulation intervention

Parents of infants in the rubbing group were asked to rub the infant’s anterior and/or lateral thigh before, during and after the injections. For practical reasons, this meant that the parent usually used the thumb of their contralateral hand to rub the infant’s leg just above the knee in a circular or back-and-forth motion while the rest of the fingers and palm rested around the infant’s knee. The parent was told to rub hard enough for the infant to feel it but not enough to cause distress. The parent was instructed to stroke the thigh for 15 seconds before, during and for up to 15 seconds after their infant received the injection although they were free to stop at any time. They were asked to refrain from directly rubbing the injection area.

2.7 Outcome measures

2.7.1 Primary outcome

2.7.1.1 MBPS

The primary outcome was acute pain, as assessed by the MBPS. The mean score for both injections was used for the analysis.
A trained observer scored MBPS from videotapes of infants. The rater was trained on multiple sets of 10 infants (i.e. 20 injections) of the same age as the current study. Scores were reviewed with original ratings and reasons for discrepancies were discussed with the candidate. A different set of 10 infants was scored and the process was repeated until the intra-class correlation was greater than 0.8.

For each injection, the MBPS was scored for 15 seconds immediately preceding the injection and for 15 seconds post-injection. If differences were found in baseline MBPS scores, the post-injection scores would have been adjusted statistically. It was expected that the injection itself would last one second or less based on a previous study using the same injection technique, so this phase was not assessed.

As a quality check on outcome assessment, 25% of infant pain scores were rated by a second person and inter-rater reliability using an intraclass correlation coefficient was calculated to determine reliability of the rater. The second rater was trained in the same manner as the first. Four DVDs were randomly selected by the candidate (tapes from procedures were transferred to DVDs for ease of coding) and procedures were coded until data for 30 infants were obtained.

### 2.7.2 Secondary outcomes

1. **Visual analog scale**

Parents and the candidate (research assistant) assessed injection pain in real time and from videorecordings, respectively, using a VAS (a 10 cm horizontal line is anchored with “no pain” on the left side and “worst pain ever” on the right side; see Appendix G). Parents completed this within one minute of each injection.

Observer-assessed VAS scores have been criticized for a lack of consistently strong indicators of validity and reliability, and absence of evidence of intra-rater reliability. However, more recent data demonstrated good intra-rater reliability for clinicians and research assistants. Since the VAS is inexpensive, easy to use, provides efficacy data if videorecording equipment fails and could support findings in the MBPS, it was included in this trial.
2.7.2.2 Cry duration

Cry duration was determined from videorecordings in one second increments for the duration of each injection procedure by a third rater. Cry duration has been used to test effectiveness of interventions in other studies of pain during immunization. Cry was defined as audible vocalization in the presence of facial grimacing. Any cry that occurred during the time frame described was recorded, not just the duration of the first cry; therefore, if an infant cried for 10 seconds, stopped for 7 seconds, cried again for 13 seconds, and then stopped, they would have a crying time of 23 seconds.

2.7.2.3 Treatment fidelity

To determine if the proposed intervention was performed by parents, videorecordings were reviewed. They were coded by the third rater (mentioned above) in 5 second increments for 15 seconds before and after each immunization to assess if parents rubbed the leg of their infant.

2.7.2.4 Measure of Adult and Infant Soothing and Distress (MAISD)

The Measure of Adult and Infant Soothing and Distress (MAISD) tool was used to describe and quantify parent behaviours during the procedure since they could not be standardized. A trained observer (the third rater, mentioned above) scored the MAISD scale from videotapes of the procedure. The MAISD scale is a tool developed in infants and children aged 6 weeks to 22 months to assess behaviours of parent, child and nurse during immunization. Behaviours included in the scale were: distraction, offer toy, offer pacifier, offer food, nursing, physical comfort, rocking and verbal reassurance. Behaviours were coded as present or absent in five second segments of time throughout the procedure. Inter-rater agreement was assessed in approximately 26% of the sample used to develop the scale. A kappa coefficient of 0.66 to 1.00 was found. The lower kappas occurred when behaviours being assessed had low base rates. MAISD is similar to the well-established CAMPIS, CAMPIS-R and CAMPIS-SF tools which were developed in older children who have verbal ability. The MAISD tool can also be
used to assess infant behaviours and the MAISD score of infant distress has positive correlation
with the MBPS (r = 0.44, p < 0.001).60

In this study, videorecordings were coded in 5 second increments for 15 seconds before and after
each injection. The tool was altered for the purposes of this trial: 1) any touch other than
rubbing the infant’s leg was captured under the category of physical comfort; 2) the category of
distraction was divided into verbal and non-verbal components and reported separately. In both
instances, the changes were made to account for the interventions in the trial: rubbing an infant’s
leg and verbally distracting them. Separating the behaviours and verbalizations allowed us to see
if the behaviours other than those coached as part of the intervention occurred at different rates in
the groups in the study.

A second parent was present for immunization in a subset of procedures. Where it was evident
to the MAISD coder that a second parent was present in the room (since they might not be
visible in the videorecording), behaviours for the second parent were coded.

A clinician was present in the room to perform the injections. Nurses were given no instructions
about how to interact with the parent and infant, and their behaviours were also coded with
MAISD. An extra behaviour was created for nurses which was not part of MAISD: procedural
talk. Comments such as “One, two, three, ow” said prior to the injection would get coded in this
category. These verbalizations would not have been coded in the original MAISD tool and we
thought it might be valuable to track for this set of clinicians.

Incidence of behaviours was calculated for each type of adult (parent holding, second parent and
clinician). Occurrence of the behaviours was coded as yes/no for the 15 second epochs. Those
that occurred in at least 20% of the adults were compared between treatment and control groups.
For behaviours that occurred in at least 50% of adults, the duration of the behaviours were
compared.

2.7.2.5 Parent acceptability of interventions

Measure of patient preferences and values is important when developing new treatments and
health strategies to ensure efforts are focused in the right areas and to learn if successful
interventions will be accepted by patients. For the current study, this was assessed by a parental survey administered by the candidate. The parent who held the infant during the immunization procedure (and performed either verbal distraction, or verbal distraction and tactile stimulation) was asked a series of questions by the candidate and their answers were recorded on a standard form (Appendix D).

2.8 Demographic data

Demographic data was obtained by interviewing the parent who attended the well-baby visit with the infant. Ethnicity, birthdate, gestational age at birth, delivery method, etc., were recorded as reported by the parent. In certain circumstances, the patient chart was consulted (e.g. dates of other immunizations, current weight). Information was recorded on a standard form developed by the candidate (Appendix E). Minimal information (age, weight, sex, reason for refusal) was also collected (with consent) from parents who declined to participate. This was done to determine if those infants were similar to the ones who participated in the study.

2.9 Sample size calculation

The candidate calculated the sample size using the Trial Protocol Tool (available at www.practihc.net/index.htm). A sample of 56 per group was calculated to demonstrate a 15% difference in MBPS pain scores assuming a standard deviation of 1.5, 80% power and two-sided alpha level of 0.05. A MBPS value of 5.6 was used to determine the 15% change (0.8 point on MBPS). This score was observed in the group receiving a fast injection without aspiration in a study comparing injection techniques, and was expected to be similar to the score in the control group in the present study because the fast injection technique without aspiration was being used. A 15% reduction in pain was considered clinically important to parents. A total sample size of 60 infants per group (120 altogether) was planned to account for drop-outs, missing data and equipment malfunction.
2.10 Compliance and missing data

The primary analysis was done by intent-to-treat principles. Missing data points were not included in the analysis (i.e. data were not imputed). If a large drop-out or cross-over occurred, an on-treatment analysis was planned.

All data were entered into Excel spread sheets by undergraduate students or the candidate. All data (100%) were checked for accuracy at a later date by the candidate and an undergraduate student working together.

2.11 Statistical analysis

The candidate performed all statistical analyses on the data.

2.11.1 Primary objective

The mean of the MBPS scores for both injections were compared between groups using a t-test. There is support for treating MBPS data as interval data\textsuperscript{66, 67} and this was done for the current study.

2.11.2 Secondary objectives

An \textit{a priori} secondary analysis of the primary outcome was performed: the percent of infants experiencing no pain (defined as MBPS scores of 2 or less) during the post-injection phase in each group was compared using a Fisher’s exact test. A score of 2 is obtained for an infant with a neutral expression and who is not crying (see Appendix A).

Pain outcomes (MBPS, VAS, and duration of crying) during each vaccine injection were separately analyzed using t-tests. Exploratory regression analyses were planned if differences in baseline characteristics were noticed. Presence of cry at baseline and post-injection were compared using $\chi^2$-tests. Individual questions on the parent questionnaire of acceptability of the
intervention were compared using χ²-tests. A significance level of 0.05 was used. Data analysis was performed on Statistical Package for the Social Sciences (SPSS) version 19.

2.11.3 Baseline characteristics

In order to ensure that infants in each group were similar at baseline, characteristics were compared using t-tests, χ²- or Fisher’s exact tests where appropriate (continuous or categorical data). Behaviour between adults and infants in the procedure room were also coded to identify any differences. Occurrence of MAISD behaviours and verbalizations were compared using χ²-tests and the duration of the MAISD items was compared using t-tests. A significance level of 0.05 was used. Data analysis was performed on Statistical Package for the Social Sciences (SPSS) version 19.

2.11.4 Multiplicity of testing

Multiple comparisons between the two study groups were made to assess pain outcomes (continuous variables: MBPS scores, VAS by parent, VAS by research assistant, cry duration; and categorical variables: presence of pain [MBPS > 2] and cry). In addition, because there were many baseline characteristics collected, many statistical tests were done to determine whether there were differences between groups at baseline that might influence outcomes. Multiplicity, or multiple testing of significance, may be a concern in this type of situation. When multiple tests are conducted, the risk of type 1 error increases (i.e. finding a difference when none exists). Using an alpha level of 0.05, one expects to find a significant difference at least 5% of time by chance alone, so 20 tests in a study would contain, on average, one false positive.

To avoid type 1 error, the alpha level is sometimes adjusted according to a formula. One example is the Bonferroni correction which divides the declared alpha level (e.g. 0.05) by the number of comparisons to obtain a new alpha level that is required to determine significance. The use of this and similar strategies can lead to loss of power and type 2 error (false negative) and has been debated as overly conservative by some. When considering outcome assessment, highly correlated outcomes (e.g. MBPS score and cry duration) are expected in
clinical practice and, therefore, some have argued that alpha levels should not be adjusted downwards in this situation.\textsuperscript{69} There was no \textit{a priori} plan for alpha adjustment in the current study as the MBPS was considered the primary outcome and conclusions were based on the results obtained from the MBPS.

2.11.5 Interim analysis

No interim analyses were performed.
Chapter 3

3 Results

3.1 Patient flow

Figure 1: Participant flow

Eligible and approached for participation (n=179)

Declined to participate (n=58)
Unable to complete consent process due to children distracting parent (n=1)

Randomized (n=120)

Allocated to intervention (n=60)
Received intervention (n=60)

Allocated to control group (n=60)
Did not receive intervention (n=60)

Analyzed (n=60)

Analyzed (n=60)
Infants and their parents were enrolled between August 6, 2009 and November 16, 2010. A total of 179 infant-parent dyads were approached and 58 declined. Of those consenting, one parent was unable to complete the training required before the procedure due to older children accompanying her at the visit who were distracting. Their visit occurred at the end of the work day and the nurse responsible for giving the vaccine needed to leave the office; therefore, it was decided that no further attempts at training would be made and the baby did not participate.

3.1.1 Characteristics of consenting versus non-consenting infants

Infants who declined participation were not different than those who participated when compared for age and weight (p > 0.05). Reasons for not participating are described in Table 2.
Table 2: Demographic characteristics of participants and non-consenting infants

<table>
<thead>
<tr>
<th></th>
<th>Participated n=120</th>
<th>Non-participating n=59</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, number (%)</td>
<td>61 (51)</td>
<td>36 (61)</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>7.3 (1.2)</td>
<td>7.0 (0.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Age when approached, weeks (SD)</td>
<td>21 (5)</td>
<td>21 (4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Reason for refusal, number (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent was in a hurry</td>
<td>26 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent wanted simultaneous injection of both vaccines</td>
<td>22 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother wanted to breastfeed during procedure</td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent didn’t want infant to receive oral sucrose</td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2 Characteristics of groups

3.2.1 Baseline characteristics

One hundred and twenty infant-parent dyads were randomized; sixty received the tactile stimulation intervention and sixty served as controls. Demographic data are shown in Table 3. There were no significant differences between groups. The mean infant postnatal age was 21 weeks in each group. Mean weight was 7.4 kg in the intervention group versus 7.1 kg in the
control group. The number of males in each group was 35 versus 26. Mothers attended with their infant for 58 of the visits in each group.

Table 3: Baseline characteristics

<table>
<thead>
<tr>
<th>Infant characteristics</th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg (SD)</td>
<td>7.4 (1.2)</td>
<td>7.2 (1.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Male sex, number (%)</td>
<td>35 (58)</td>
<td>26 (43)</td>
<td>0.10</td>
</tr>
<tr>
<td>Attending for 4 month visit, number (%)</td>
<td>41 (68)</td>
<td>44 (73)</td>
<td>0.55</td>
</tr>
<tr>
<td>Age at visit, weeks (SD)</td>
<td>21 (5)</td>
<td>21 (5)</td>
<td>0.59</td>
</tr>
<tr>
<td>Premature birth, number (%)</td>
<td>3 (5)</td>
<td>5 (8)</td>
<td>0.72</td>
</tr>
<tr>
<td>Gestational age at birth, weeks (SD)</td>
<td>40 (2)</td>
<td>39 (2)</td>
<td>0.44</td>
</tr>
<tr>
<td>Breastfeeding (full or partial), number (%)</td>
<td>45 (75)</td>
<td>43 (72)</td>
<td>0.68</td>
</tr>
<tr>
<td>Medical condition, number (%)</td>
<td>6 (10)</td>
<td>10 (17)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ethnicity, number (%)</td>
<td>Tactile stimulation n=60</td>
<td>Standard care n=60</td>
<td>p</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------</td>
<td>--------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Caucasian</td>
<td>39 (65)</td>
<td>42 (70)</td>
<td>0.56§</td>
</tr>
<tr>
<td>Afro-American</td>
<td>5 (8)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (7)</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (20)</td>
<td>10 (17)</td>
<td></td>
</tr>
</tbody>
</table>

| Early pain experience         |                          |                    |     |
| Vaginal delivery, number (%)  | 41 (68)                  | 38 (63)            | 0.56|
| Forceps at delivery, number (%)| 1 (2)                    | 1 (2)              | 1.00|
| Vacuum at delivery, number (%)| 2 (3)                    | 4 (7)              | 0.68|
| Circumcised males, number (% of males)| 13 (37)               | 8 (31)            | 0.60|
| Hospitalized >1 week at birth, number (%)| 1 (2)                  | 1 (2)              | 1.00|
| Hospitalized since birth, number (%)| 3 (5)                   | 3 (5)              | 1.00|
| Extra immunizations (in addition to routine), ** number of infants (%)| 6 (10)                 | 2 (3)              | 0.27|

§ Versus all others in grouping.

** Hepatitis B vaccine, meningococcal C conjugate vaccine, influenza vaccine (seasonal and pandemic H1N1), palivizumab (respiratory syncytial virus prophylaxis).
### Family characteristics

Attending visit with infant:

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>36 (60)</td>
<td>34 (57)</td>
<td>1.00††</td>
</tr>
<tr>
<td>Father</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>22 (37)</td>
<td>24 (40)</td>
<td></td>
</tr>
</tbody>
</table>

Siblings, number (%)

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35 (58)</td>
<td>28 (47)</td>
<td>0.20‡‡</td>
</tr>
<tr>
<td>1</td>
<td>21 (35)</td>
<td>25 (42)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (7)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

### Procedure characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby held by mother, number (%)</td>
<td>44 (73)</td>
<td>52 (87)</td>
<td>0.07</td>
</tr>
<tr>
<td>Acetaminophen or ibuprofen before injection, number (%)</td>
<td>13 (22)</td>
<td>17 (28)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

---

†† Comparing mother or both versus father alone.

‡‡ Versus all others in grouping.
<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant positioned for injections with some restraint of arms or legs, number (%)</td>
<td>50 (83)</td>
<td>52 (87)</td>
<td>0.61</td>
</tr>
<tr>
<td>Time since last sleep, HH:MM (SD)</td>
<td>2:08 (1:05)</td>
<td>2:18 (1:06)</td>
<td>0.42</td>
</tr>
<tr>
<td>Time since last food, HH:MM (SD)</td>
<td>1:32 (1:53)</td>
<td>1:34 (2:03)</td>
<td>0.94</td>
</tr>
<tr>
<td>Time from sucrose administration to first injection, MM:SS (SD)</td>
<td>2:21 (0:43)</td>
<td>2:22 (0:41)</td>
<td>0.93</td>
</tr>
<tr>
<td>Time from sucrose administration to second injection, MM:SS (SD)</td>
<td>4:18 (1:12)</td>
<td>4:09 (0:55)</td>
<td>0.42</td>
</tr>
<tr>
<td>Shorter than standard needle used for injection, number (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Synflorix™ brand of PCV, number (%)§§</td>
<td>30 (50)</td>
<td>31 (52)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**Clinician characteristics**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians participating, number</td>
<td>13</td>
<td>13</td>
<td>1.00</td>
</tr>
<tr>
<td>Clinician experience, years (SD)</td>
<td>22 (12)</td>
<td>23 (11)</td>
<td>0.84</td>
</tr>
<tr>
<td>Clinician experience with fast injection technique, mean years (SD)</td>
<td>1.4 (1.1)</td>
<td>1.5 (1.4)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

§§ PCV vaccine supplied by the provincial government changed from Prevnar® to Synflorix™ during the study. Anecdotal reports by the clinicians suggested it had a comparable level of pain response when given to infants.
3.2.2 Treatment fidelity

Sixty infant-parent dyads were randomized to receive the tactile stimulation intervention. As can be seen in Table 4, 59 parents rubbed their infant’s leg for at least one phase of the immunization procedure.

For parents who rubbed their infant’s leg, the time engaged in this activity for 15 seconds before and after each injection is reported in Table 5.

<table>
<thead>
<tr>
<th>Item</th>
<th>Before injection</th>
<th>p</th>
<th>After injection</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tactile stimulation n=60</td>
<td>Standard care n=60</td>
<td></td>
<td>Tactile stimulation n=60</td>
</tr>
<tr>
<td>Rub leg, injection 1, number (%)</td>
<td>57 (95)</td>
<td>2 (3)</td>
<td>&lt;0.01</td>
<td>56 (93)</td>
</tr>
<tr>
<td>Rub leg, injection 2, number (%)</td>
<td>55 (92)</td>
<td>0</td>
<td>&lt;0.01</td>
<td>51 (85)</td>
</tr>
<tr>
<td>Rub leg, injection 1 and 2 combined, number (%)</td>
<td>59 (98)</td>
<td>2 (3)</td>
<td>&lt;0.01</td>
<td>59 (98)</td>
</tr>
</tbody>
</table>
Table 5: Time spent rubbing the leg

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation</th>
<th>Standard care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubbing leg before, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>12 (4)</td>
<td>5(0)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>14 (3)</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rubbing leg after, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>12 (4)</td>
<td>5 (-)&lt;sup&gt;†††&lt;/sup&gt;</td>
<td>0.07</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>11 (5)</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

3.2.3 MAISD

Behaviours and vocalizations for adults were captured using MAISD. All components of the MAISD were sought but most were not observed in the majority of infant-parent dyads.

Table 6 provides incidence and statistical comparisons of each of the categories for the parent holding the baby that occurred at least 20% of the time. The remainder of behaviours can be found in Appendix F. For almost all comparisons in each 15 second epoch, there were no statistical differences in behaviour between groups. The two exceptions were: 8 more parents in the intervention group offered verbal distraction after injection 2 (54 versus 46, p = 0.05) and 2) 9 more parents in the control group offered physical comfort after injection 2 (8 versus 17, p = 0.04).

*** 2 infants-parent dyads were coded to have tactile stimulation for 5 seconds each prior to the injection.

††† 1 infant-parent dyad was coded to have tactile stimulation for 5 seconds after the injection.
Mean duration of behaviours that occurred in at least 50% of infants in at least one group are reported in Table 7. Only verbal distraction met that criterion. No statistical difference was seen between groups for the amount of time spent verbally distracting infants.

A second parent’s behaviours were coded for 14 cases. Since none of the behaviours or verbalizations occurred for at least 20% of parents, they are not presented here but can be found in Appendix F.

All procedures were coded for clinician behaviours and verbalizations. The incidence of clinician MAISD components that occurred at least 20% of the time is recorded in Table 8. Since no component of clinician MAISD occurred in at least 50% of infants, no duration of behaviours has been reported. The full table of observed behaviours can be found in Appendix F.
Table 6: Incidence of MAISD behaviours occurring in at least 20% of parents holding baby

<table>
<thead>
<tr>
<th>Item</th>
<th>Before injection</th>
<th></th>
<th></th>
<th>After injection</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tactile stimulation n=60</td>
<td>Standard care n=60</td>
<td>p</td>
<td>Tactile stimulation n=60</td>
<td>Standard care n=60</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Distraction (verbal), injection 1, number (%)</td>
<td>54 (90)</td>
<td>57 (95)</td>
<td>0.49</td>
<td>56 (93)</td>
<td>54 (90)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Distraction (verbal), injection 2, number (%)</td>
<td>52 (87)</td>
<td>53 (88)</td>
<td>0.78</td>
<td>54 (90)</td>
<td>46 (77)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Distraction (verbal), injection 1 and 2 combined, number (%)</td>
<td>59 (98)</td>
<td>59 (98)</td>
<td>1.00</td>
<td>57 (95)</td>
<td>55 (92)</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Physical comfort, injection 1, number (%)</td>
<td>2 (3)</td>
<td>4 (7)</td>
<td>0.68</td>
<td>9 (15)</td>
<td>8 (13)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Physical comfort, injection 2, number (%)</td>
<td>6 (10)</td>
<td>4 (7)</td>
<td>0.51</td>
<td>8 (13)</td>
<td>17 (28)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Item</td>
<td>Before injection</td>
<td>After injection</td>
<td>p</td>
<td>Tactile stimulation n=60</td>
<td>Standard care n=60</td>
<td>p</td>
<td>Tactile stimulation n=60</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>-----</td>
<td>--------------------------</td>
<td>--------------------</td>
<td>-----</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Physical comfort, injection 1 and 2 combined, number (%)</td>
<td>6 (10)</td>
<td>8 (13)</td>
<td>0.57</td>
<td>16 (27)</td>
<td>22 (37)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Verbal reassurance, injection 1, number (%)</td>
<td>4 (7)</td>
<td>0</td>
<td>0.12</td>
<td>8 (13)</td>
<td>13 (22)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Verbal reassurance, injection 2, number (%)</td>
<td>5 (8)</td>
<td>7 (12)</td>
<td>0.76</td>
<td>23 (38)</td>
<td>14 (23)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Verbal reassurance, injection 1 and 2 combined, number (%)</td>
<td>8 (13)</td>
<td>7 (12)</td>
<td>0.12</td>
<td>25 (42)</td>
<td>21 (35)</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>
Table 7: Duration of MAISD behaviours with incidence >50% – parent holding baby

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation</th>
<th>Standard care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal distraction before, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>11 (4)</td>
<td>11 (4)</td>
<td>0.26</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>12 (4)</td>
<td>12 (4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Verbal distraction after, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>12 (4)</td>
<td>12 (4)</td>
<td>0.53</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>11 (4)</td>
<td>12 (4)</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Table 8: Incidence of MAISD behaviours – nurse

<table>
<thead>
<tr>
<th>Item</th>
<th>Before injection</th>
<th></th>
<th>p</th>
<th>After injection</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tactile stimulation</td>
<td>n=60</td>
<td>Standard care</td>
<td>n=60</td>
<td></td>
</tr>
<tr>
<td>Distraction (verbal), injection 1, number (%)</td>
<td>3 (5)</td>
<td>6 (10)</td>
<td>0.49</td>
<td>2 (3)</td>
<td>4 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Distraction (verbal), injection 2, number (%)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>1.00</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Distraction (non-verbal), injection 1, number (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Distraction (non-verbal), injection 2, number (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>1.00</td>
<td>1 (2)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Verbal reassurance, injection 1, number (%)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.00</td>
<td>13 (22)</td>
<td>13 (22)</td>
<td>1.00</td>
</tr>
<tr>
<td>Verbal reassurance, injection 2, number (%)</td>
<td>6 (10)</td>
<td>5 (8)</td>
<td>0.75</td>
<td>14 (23)</td>
<td>9 (15)</td>
<td>0.25</td>
</tr>
<tr>
<td>Procedural talk, injection 1, number (%)</td>
<td>12 (20)</td>
<td>8 (13)</td>
<td>0.33</td>
<td>16 (27)</td>
<td>18 (30)</td>
<td>0.69</td>
</tr>
<tr>
<td>Procedural talk, injection 2, number (%)</td>
<td>19 (32)</td>
<td>13 (22)</td>
<td>0.22</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
3.3 Outcomes of study: effect of tactile stimulation during immunization

3.3.1 MBPS scores

Outcome data are shown in Table 9. The mean MBPS score for injection 1 and injection 2 did not differ between groups. The tactile stimulation group received a rating of 8.2 and the control group received a rating of 8.0 (p = 0.57).

The MBPS did not differ at baseline (prior to injection 1 and 2, p = 0.70 and p = 0.17 respectively).

After injection, MBPS scores did not differ between groups: 7.6 versus 7.2 (p = 0.30) for the first injection and 8.8 versus 8.9 for the second injection (p = 0.50) for the tactile stimulation and control groups, respectively.

MBPS scores were dichotomized into two categories for an a priori analysis: the number of infants who scored 2 or less, representing no pain, and those who scored more than 2, representing infants who had pain. The results are presented in Table 10. No statistical difference was found in the number of infants who had pain before or after either injection.
Table 9: MBPS scores

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p³³³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (15 seconds before injection), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>3.1 (2.1)</td>
<td>2.9 (2.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>4.3 (2.3)</td>
<td>4.9 (2.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Average both injections</td>
<td>3.7 (1.8)</td>
<td>3.9 (2.0)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Post injection (15 seconds after injection), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>7.6 (1.8)</td>
<td>7.2 (2.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>8.8 (0.9)</td>
<td>8.9 (0.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Average both injections</td>
<td>8.2 (1.1)</td>
<td>8.0 (1.3)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

³³³ t-test.
Table 10: Presence of pain (MBPS score >2)

|                           | Tactile stimulation n=60 | Standard care n=60 | p
§§§                  |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of pain at baseline (15 seconds before injection), number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>18 (30)</td>
<td>15 (25)</td>
<td>0.54</td>
</tr>
<tr>
<td>2nd injection</td>
<td>40 (67)</td>
<td>42 (70)</td>
<td>0.70</td>
</tr>
<tr>
<td>Presence of pain (15 seconds after injection), number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>59 (98)</td>
<td>58 (97)</td>
<td>1.00</td>
</tr>
<tr>
<td>2nd injection</td>
<td>60 (100)</td>
<td>60 (100)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

3.3.2 Reliability of MBPS scores

Scores obtained by a second rater were compared to the first rater’s scores for 30 infants. Fifteen infant-parent dyads came from the intervention group, and 15 came from the control group. The intra-class correlation coefficient calculated on 25% of the MBPS scores was 0.91 (95% confidence interval 0.88, 0.94, p < 0.01).

§§§ \( \chi^2 \) or Fisher’s exact test.
3.3.3 Visual analog scales

3.3.3.1 Parents

No statistical difference was seen between groups for parent global pain assessment measured by a 100 mm VAS (Table 11). No differences were seen in pain ratings prior to each injection or after each injection. Averages of injection 1 and 2 were also not statistically different.

Table 11: Parent VAS****

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation</th>
<th>Standard care</th>
<th>p††††</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=60</td>
<td>n=60</td>
<td></td>
</tr>
<tr>
<td>Baseline, mean mm (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>0.18</td>
</tr>
<tr>
<td>2nd injection</td>
<td>20 (17)</td>
<td>18 (17)</td>
<td>0.50</td>
</tr>
<tr>
<td>Average both injections</td>
<td>11 (10)</td>
<td>9 (9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Post injection, mean mm (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>47 (21)</td>
<td>42 (24)</td>
<td>0.18</td>
</tr>
<tr>
<td>2nd injection</td>
<td>72 (23)</td>
<td>65 (23)</td>
<td>0.08</td>
</tr>
<tr>
<td>Average both injections</td>
<td>60 (20)</td>
<td>53 (22)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**** Scale 0 – 100 mm.
†††† t test.
3.3.3.2 Research assistant

No statistical difference in pain rating was seen between the tactile stimulation and standard care groups prior to either injection (Table 12). No statistical difference was seen between pain ratings after each injection, or for the average of both injections.

Table 12: Research assistant VAS

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p$^{	ext{§§§§}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean mm (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>1 (2)</td>
<td>0 (2)</td>
<td>0.63</td>
</tr>
<tr>
<td>2nd injection</td>
<td>8 (12)</td>
<td>7 (9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Average both injections</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Post injection, mean mm (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>37 (19)</td>
<td>31 (19)</td>
<td>0.07</td>
</tr>
<tr>
<td>2nd injection</td>
<td>63 (18)</td>
<td>60 (17)</td>
<td>0.35</td>
</tr>
<tr>
<td>Average both injections</td>
<td>50 (17)</td>
<td>46 (16)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

$^{	ext{‡‡‡‡}}$ Scale 0 – 100 mm.

§§§§ t test.
3.3.4 Cry duration

No statistical difference was seen between treatment and intervention groups for cry duration before either injection (Table 13). No difference was seen between groups after each injection or for the average of both injections measured for 15 second, 30 second and 60 seconds after injection. Averages of injection 1 and 2 were also not statistically different.

No difference was seen for incidence of cry between treatment and intervention groups before either injection, or after either injection during the first 15 seconds, 30 seconds or 60 seconds (Table 14).

Table 13: Cry duration

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p *****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry duration at baseline (15 seconds before injection), seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0.50</td>
</tr>
<tr>
<td>2nd injection</td>
<td>2 (5)</td>
<td>3 (5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Average both injections</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

****

* t test.
<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry duration, 15 seconds after injection, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>9 (5)</td>
<td>8 (6)</td>
<td>0.26</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>13 (2)</td>
<td>13 (2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Average both injections</td>
<td>11 (4)</td>
<td>11 (3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cry duration, 30 seconds after injection, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>14 (11)</td>
<td>12 (11)</td>
<td>0.32</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>25 (7)</td>
<td>24 (6)</td>
<td>0.84</td>
</tr>
<tr>
<td>Average both injections</td>
<td>20 (8)</td>
<td>19 (7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cry duration, first minute after injection, seconds (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
<td>20 (19)</td>
<td>20 (20)</td>
<td>0.87</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
<td>41 (17)</td>
<td>38 (16)</td>
<td>0.32</td>
</tr>
<tr>
<td>Average both injections</td>
<td>31 (15)</td>
<td>29 (15)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*****t-test.
Table 14: Incidence of cry

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>p †††††</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of cry at baseline (15 seconds before injection), number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>9 (15)</td>
<td>8 (13)</td>
<td>0.80</td>
</tr>
<tr>
<td>2nd injection</td>
<td>19 (32)</td>
<td>20 (33)</td>
<td>0.85</td>
</tr>
<tr>
<td>Incidence of cry, 15 seconds after injection, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>52 (87)</td>
<td>47 (78)</td>
<td>0.23</td>
</tr>
<tr>
<td>2nd injection</td>
<td>60 (100)</td>
<td>59 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>Incidence of cry, 30 seconds after injection, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>52 (87)</td>
<td>47 (78)</td>
<td>0.23</td>
</tr>
<tr>
<td>2nd injection</td>
<td>60 (100)</td>
<td>59 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>Incidence of cry, first minute after injection, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st injection</td>
<td>52 (87)</td>
<td>47 (78)</td>
<td>0.23</td>
</tr>
<tr>
<td>2nd injection</td>
<td>60 (100)</td>
<td>59 (98)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

††††† t test.
3.3.5 Adverse events

No adverse events were reported in the study.

3.3.6 Parent acceptability of intervention

No statistical differences were seen between groups for answers to questions about the procedures in the study. Results are presented in Table 15. All respondents found the information sheet somewhat or very easy to understand. For the group assigned to tactile stimulation, 76% found it somewhat or very easy to perform the intervention compared to 62% in the group assigned to tactile stimulation (p = 0.12). Only 53% in each group thought their infant benefited from the parent’s actions. Despite this, 88% in the tactile stimulation group said they would do it again, and 85% and 87% of parents in the intervention and control groups, respectively, would use verbal distraction in the future.
Table 15: Responses to survey by parent holding infant

<table>
<thead>
<tr>
<th></th>
<th>Tactile stimulation n=60</th>
<th>Standard care n=60</th>
<th>( \chi^2 ) test.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers responding, number (%)</td>
<td>44 (73)</td>
<td>51 (85)§§§§§</td>
<td>0.12</td>
</tr>
<tr>
<td>Somewhat or very easy to understand the Fact Sheet, number (%)</td>
<td>60 (100)</td>
<td>60 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Somewhat or very easy to do what the Fact Sheet suggested, number (%)</td>
<td>45 (76)******</td>
<td>37 (62)</td>
<td>0.12</td>
</tr>
<tr>
<td>Parent thought infant benefited from what parent did, number (%)</td>
<td>32 (53)</td>
<td>32 (53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Parent will give sucrose in the future, number (%)</td>
<td>56 (93)</td>
<td>49 (82)</td>
<td>0.10</td>
</tr>
<tr>
<td>Parent will rub leg in the future, number (%)</td>
<td>53 (88)</td>
<td>n/a</td>
<td>-</td>
</tr>
<tr>
<td>Parent will use distracting talk techniques in the future, number (%)</td>
<td>51 (85)</td>
<td>52 (87)</td>
<td>0.79</td>
</tr>
<tr>
<td>Parent will sing in future, number (%)</td>
<td>10 (17)</td>
<td>8 (13)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

§§§§§ 52 mothers held babies in this group but for one survey, responses were given by both parents.

****** n = 59 for this question only.
Chapter 4

4 Discussion

4.1 Summary of results

To our knowledge, this is the first study to evaluate parent-led tactile stimulation for pain reduction in infants undergoing immunization injections. No significant effects were demonstrated on infant pain response. This was evident from the primary outcome, the MBPS, using mean of scores from both injections, as well as from individual injections. Results were consistent for all secondary outcomes of pain, including: VAS ratings from parents and the research assistant, cry duration, and dichotomous categories of pain/no pain (using MBPS) and cry/no cry. The majority of parents (60%) reported that the information they were given was easy to understand; however, the requested behaviour was not easy for 24% of the group allocated to the tactile stimulation group and 38% of the group allocated to the control group (p = 0.12). Only 53% of the parents felt their infant benefited from their actions during the injection procedure.

In addition, relatively high pain scores were observed for infants in both arms of the study (mean, 8.2 versus 8.0, p = 0.57), despite the fact that they all received pain relieving interventions (sucrose, holding, fast injection without aspiration).

These results are inconsistent with previous studies of tactile stimulation to reduce procedural pain. A previous study including 105 children aged 4 to 6 years found less self-reported pain (Oucher scale, †††††† 0 - 10) from the intervention group, which was either rubbing the leg near the injection site or having the child blow bubbles.20 Less pain occurred in the two interventions (1.89 [rubbing] and 2.00 [bubbles], versus 2.89 in the control group, p = 0.01). The method of tactile stimulation in the current study was most similar to tactile stimulation in this study, except that the investigator administered tactile stimulation, rather than the parent, and a different person administered the injection.

†††††† Oucher is a vertical scale with marks of 0 to 10 and six photographs of a child’s face beside the even numbers representative of that amount of pain at each point. The child picks the face that matches how they feel.
Four studies of tactile stimulation in adults undergoing injections and one study of needle insertion without injection all found it was effective to reduce pain compared to no tactile stimulation. The magnitude of pain reduction varied from 0.79 cm to 2.55 cm on a 10 cm scale. Like the studies in children, investigators or clinicians administered the intervention.

It is possible the lack of blinding in these earlier studies may have biased the results towards a larger effect. Adult participants who consented to enroll in studies might have expectations about the effectiveness of tactile stimulation and are also responsible for rating their pain. In the current study, parents and the outcome assessor were blinded to the treatment being studied and study hypotheses.

One study in 23 neonates showed that rubbing the ipsilateral leg for two minutes prior to heel lance reduced pain by 2 points on the NIPS (0 - 10 points) using assessors blinded to the intervention. A second heel lance study of 8 infants found a smaller decrease in transcutaneously measured oxygen levels (suggestive of less pain) in the group receiving contralateral tactile simulation, although no statistical tests were reported in the paper. While the age groups in these studies is close to the group in the current study, the procedure (heel lance) is somewhat different than an immunization injection. An injection involves piercing the skin but also causes pain when tissue is distended by the volume being injected, and may also cause pain due to the physicochemical properties of the injection liquid. On the other hand, heel lance involves cutting the skin with a small blade and squeezing the heel to obtain blood.

It is interesting that 53% of parents felt their behaviour (rubbing the skin and/or distracting the infant) did not reduce their infant’s pain, but more than 85% of them were willing to do the same activity in the future. This may reflect parent desire to want pain reducing strategies, and their willingness to use methods that they perceive to be harmless. It would seem that if disseminated, these behavioural strategies would have a high acceptability among parents.

### 4.2 Potential reasons for lack of effect from tactile stimulation

This section discusses possible reasons for why tactile stimulation did not reduce pain in this population. Reasons are grouped according to parent factors and clinician factors.
4.2.1 Parent factors

4.2.1.1 Administration of tactile stimulation

The parent holding the infant was trained to administer tactile stimulation near the injection site and the parent practiced the technique and verbal distraction with their infant prior to the procedure. Parents were instructed to rub the skin just above the knee. No attempt was made to standardize the amount of pressure applied to the leg. Training was performed rapidly in a manner that could be consistent with a busy primary care practice. A more thorough training might have produced different results, but the results might not have been reproducible in practice.

Two prior studies of tactile stimulation in adults that found a benefit for the intervention employed technology to standardize and measure the amount of pressure delivered. One used a dolorimeter to train the clinician prior to the study to ensure a standard amount of pressure was delivered at each injection;\textsuperscript{18} in the other study, a pressure sensing device was placed between the clinician’s thumb and the participant’s skin to measure each application of pressure prior to the injection.\textsuperscript{19} Parents in the current study may have been stressed because their infant was being immunized and experiencing pain, and may have found it difficult to tailor tactile stimulation to their infant’s needs (e.g. they might have rubbed the skin too firmly or too lightly). Since the current study did not employ any method to train parents to use a standard amount of pressure, and did not measure the amount of pressure applied, it is not known if they consistently applied a similar amount of pressure. It is also not known what constitutes an appropriate amount of pressure. These issues could account for some of the lack of benefit observed in the study.

It is possible that parents participating in the study who were allocated to the intervention group were pre-occupied with the prescribed intervention and failed to comfort their infant in their usual ways. This might have occurred if they weren’t aware of their infant’s state because they focused on the intervention, or if they were aware but thought they should continue with the intervention (because they were in a study) rather than do what would have been natural for them. Although measured behaviours (from MAISD) were not different between groups (except
for one epoch of physical comfort and one of verbal distraction), it is possible that unmeasured behaviours, or the quality of behaviours, could have been different and contributed to the study results.

Parents in both groups practiced their behaviours (either rubbing and verbal distraction or just verbal distraction) with their infants prior to the study. It is possible that the extra handling that occurred with infants in the tactile stimulation group contributed to higher pain scores in the intervention group during the procedure.

The location of tactile stimulation was just above the knee on the anterior surface of the thigh. It was chosen for feasibility and logistic reasons: parents were required to hold their infant and administer the intervention; clinicians required space to work. Tactile stimulation is thought to work via the gate theory, which requires nerve impulses from noxious and non-noxious stimuli to reach the same level of the spinal cord. The intervention should be effective if the tactile stimulus occurs in the same dermatome as the injection. In infants, the anterior thigh is supplied by the L2 and L3 nerve roots. There is some overlap and the margins are not precise. So, while it is possible that rubbing was not performed close enough to the injection site to ensure the same dermatome was stimulated by both the noxious and non-noxious stimuli, some of the stimuli would be expected to reach the same level of the spinal cord. The receptive field of an individual neuron, however, is smaller than the entire dermatome and having both noxious and non-noxious stimuli occurring in the same receptive field might improve the pain reducing ability of the intervention. Having a clinician perform the intervention might facilitate tactile stimulation closer to the injection site. Light tactile stimulation directly over the injection site might also prove beneficial. A study of infants receiving DTP found massage of the injection site caused more delayed pain and swelling at the site and was related to intensity of the massage, but light touch at the site might reduce immediate pain without causing delayed pain. Despite concerns discussed, insufficient proximity of the two stimuli may not be the entire explanation for the lack of effect observed.
4.2.1.2 Distraction and comfort

Incidence of parent behaviour was not different in most categories. Physical comfort was offered to more infants in the control group after injection 2 (8 versus 17, p = 0.04). Verbal distraction after injection 2 occurred in more infants in the intervention group (54 versus 46, p = 0.05).

It is interesting that physical comfort was offered less in the intervention group after injection 2. Physical comfort could include behaviours like rubbing, massaging, patting, kissing or hugging. For the purposes of this study, rubbing the leg was not included as physical comfort. The intervention might have prevented parents from providing physical comfort after the injection because parents continued the intervention after each injection and were slower to comfort their infants (i.e. if they offered physical comfort, it occurred after the coding epoch and was not captured in this analysis). One study suggested patting, rocking and bouncing were probably helpful behaviours to reduce infant pain.\textsuperscript{49} If physical comfort helps to abort pain expression, then the parents offering more physical comfort might have infants with lower pain scores and for this study, would tend to decrease scores in the control group. It must be noted that this observation occurred in 8 of 60 dyads in the intervention group and 17 of 60 dyads in the control group (less than 30% of the sample) and this could be a chance finding so no conclusions should be drawn.

Alternatively, if rubbing the leg was considered physical comfort (and it might be perceived that way to the infant), then the treatment group received more overall physical comfort before and after the immunization despite the difference noted above, which might result in lower pain scores in the intervention group.

One concern that existed \textit{a priori} was that parents assigned to the tactile stimulation group would perform the intervention and forget to verbally distract their infants; however the amount of verbal distraction in 3 of the 4 epochs (before and after each injection) was not different, and the amount of verbal distraction after the second injection was higher in the intervention group. Therefore, this concern did not occur. Distraction tends to be associated with lower levels of infant distress\textsuperscript{49} so this might result in lower pain scores in the intervention group after injection 2 (which was not observed). The current study employed parent-led distraction in both groups and did not evaluate effectiveness of this strategy. MAISD determined that there was no
difference in the amount of parent-led distraction in each group for 3 of 4 epochs; however, the infant’s engagement in distraction was not evaluated; if different between groups, it may have impacted this study’s results. A systematic review of behavioural interventions identified two randomized controlled trials in infants and children less than 2 years and one in children aged 3-7 years that evaluated parent-led distraction and found it to be ineffective in reducing pain but was effective in reducing observer-rated distress. Therefore, even if differences in distraction rates occurred (and this occurred in only 1 of 4 epochs), these other studies would suggest that the differences are unlikely to be contributing to the results.

To summarize, for behaviours occurring in infant-parent dyads at a rate of at least 20%, only two comparisons were statistically different: more physical comfort (not including the tactile intervention) occurred after the second injection in the control group and more distraction occurred after the second injection in the treatment group. Taken together it is not likely that these behaviours had an impact on the results of the study.

4.2.2 Clinician factors

Sixteen clinicians participated in this study. Some participated only once and four participated over 10 times. There were no difference in the number who participated in each group and no differences in the nurses who had more than 10 infants in the study.

One aspect of clinician variation is sucrose administration. The study captured duration of sucrose administration and time between start of administration and injection times. No difference was found between groups for this variable. The study did not capture the method of administration: it is ideally given drop by drop on the tip of the tongue so that the infant may taste it. Although the nurses had been trained on sucrose administration, sometimes nurses were observed by the candidate to give sucrose into the side of the mouth, as one might administer medicine. Past research showed that feeding sucrose via a nasogastric tube (with no opportunity to taste) failed to produce analgesia, so it is not clear whether this action (which was not recorded as part of the study) had any impact on the results. Since it is likely that this action occurred randomly with respect to tactile stimulation, it probably did not bias the results (although it is possible that specific nurses administered it incorrectly some or all of the time).
Another aspect of operator variation was injection technique. Some factors that appeared to vary among clinicians were speed of injection, how far the needle was inserted into the skin and how the skin near the injection site was handled before and during the injection. The clinicians in this study always applied alcohol prior to injection. While injection speed was not timed, it was observed by the candidate to vary among operators and was almost never as fast as the one second time demonstrated in a study comparing two injection techniques.\(^8\) Needle insertion was another observed variable that was unexpected. Some nurses were observed to never insert the entire needle shaft into the skin to the hub. Other nurses appeared to insert to the hub sometimes, but other times inserted only part of the needle when they felt the infant was small for his/her age. Needle length used in the study was consistent with Canadian Immunization Guide recommendations.\(^74\) Some studies have found that using a longer needle resulted in less reactogenicity,\(^7\) but no studies of immediate pain of injection and needle length were found. It is also unknown if failing to rest the hub on the skin causes the needle to move more in the tissue during the injection phase (which might result in more pain). It is unclear whether this clinician behaviour affected the results. If it occurred based on infant weight for some clinicians (and weight was similar between groups) it probably did not bias the results. If it occurred always with some clinicians, then it also probably did not bias the results, since nurses contributed infants to each group in similar numbers.

Some nurses appeared to handle the skin near the injection site more than others. Again, this behaviour was not part of data collection in the study but could have influenced the results because it may have been equivalent to a tactile stimulation intervention. The candidate noted that some nurses applied pressure to the site as they swabbed the area with alcohol. Others firmly grasped the leg and squeezed it as they pierced the skin. Assuming these behaviours were specific to certain nurses, and the nurses were balanced in treatment and control groups, any effect they caused should not bias the results.

Having only one person administer the intervention is more likely to result in a standardized, reliable delivery of an intervention. It is useful in an efficacy study that seeks to determine if an intervention is effective under ideal conditions, but does not reliably translate into practice and is a reason why effectiveness trials are sometimes preferred.\(^75,76\)
Differences in operators noted above are features that were observed during the study. There may be other features to the injection procedure that were not noticed and not considered, but since clinicians contributed similar numbers of infants to the treatment and control groups, it is unlikely that their variability biased the results. Instead, the differences in practice contribute to higher variability in the results obtained and make it harder to detect a signal of effect.

4.3 Generalizability of findings

External validity, or generalizability is the ability to apply results from the study population to other populations. This section discusses some of the characteristics of this population that might influence pain outcomes.

4.3.1 Sex differences in pain expression

There was no statistical difference for the percent of males in each group: 58% in the tactile stimulation group and 43% in the control group and similar numbers of males and females were allocated to the two groups. Therefore, it is likely that results from this study can be applied to both males and females.

While the majority of adult literature indicates that females show greater response to painful stimuli, the child and infant literature is less clear. Preterm neonatal males had more negative facial expressions than females in one study, and term neonatal males were faster to cry and display facial action from pain of heel lance. Lower pain scores were associated with female sex in a study of 4 and 6 month old infants. Conversely, a study in pre-term and term neonates in the first few days after birth found more pain expression in females. Others have found no sex differences: a study of infants aged 2 weeks to 12 months found no difference in time spent crying but females had a higher pitch cry at aged 7 to 12 months. And two studies in older children found no association between sex and pain response. The area requires further study and new guidance has been provided although it is not specific to paediatrics.
4.3.2 Ethnicity and pain response

There were no statistical differences in ethnicity between groups. The entire population was 68% Caucasian, 8% Asian, 6% Afro-American, and 18% other (mainly mixed race). These proportions are similar to other large Canadian cities.\textsuperscript{83}

In the adult literature, much has been written about links between the complex relationship of ethnicity and pain.\textsuperscript{84-87} Additionally, the issue is complicated by relative contributions of biological and cultural factors and whether these differences are related to pain perception, expression or measurement. In infants, the literature is less developed. One study found Japanese-American infants were less reactive to pain than Caucasian-American infants.\textsuperscript{88} Another found Chinese-Canadian infants to be more reactive to pain than Caucasian-Canadian infants, but baseline maternal factors (education and occupation) were different and could have influenced the findings.\textsuperscript{89} Conversely, a study examining computer-assistant facial expression in neonates found no differences among ethnicities.\textsuperscript{90} This is an area requiring further study.

4.4 Pain scores compared with prior immunization pain studies

The pain scores in the current study seem to be higher than those in recent immunization studies of a similar age group using the same pain rating tool. Below is a summary of pain scores for the first injection in two other immunization studies and the present one (Table 16). The scores in the current study are numerically higher for MBPS, parent and researcher VAS, and the same or higher number of infants cried in the current study than in the other two studies. No statistical analysis has been performed on these data to determine if they are different since this was not an objective of the current study.

The Ipp (2009) study compared the order of injection of the two vaccines currently given at 2, 4 and 6 months in Ontario.\textsuperscript{9} The scores of the infants given DTaP-IPV-Hib first, as in the current study, are presented below. The Ipp (2007) study compared two injection techniques in 4 and 6 month old infants: a fast one without aspiration, and a slower, traditional injection with aspiration.\textsuperscript{8} Only the first injection (DTaP-IPV-Hib) was considered in the study, but results from both administration techniques are presented. For each of the studies by Ipp et al, the infants were held by their parent while the parent stood in front of the video camera. The
clinicians and site in the two studies are the same, and are a different location from the current study.

One important consideration is that the brand of DTaP-IPV-Hib used in the current study is different than that used in the previous two studies. It is possible this could be the source of different pain scores; however, clinicians in each of the studies have not commented about a change in the amount of pain observed when brands were switched.

There may be other factors contributing to the pain scores. The speed of injection appeared shorter in the two Ipp et al studies compared to the current study (excluding the arm of one study that used a slow injection with aspiration). The Ipp (2007) study varied both speed and aspiration when measuring pain so it was not able to determine the relative contribution of each variable to pain ratings. Since clinicians in the current study did not perform aspiration, but were observed (anecdotally) to inject somewhat slower than clinicians in the Ipp study, this suggests that speed might play an important role in pain reduction.

Parents in the current study restrained their infants on their lap, with most trapping the infant’s leg(s) between theirs, and holding the infant’s arms with their hands. This was done for practical purposes – the clinicians wanted a still leg to inject and did not want the infant to grab the needle while the clinician was performing the injection. The position was quite different in the earlier studies, where the infant’s arms and legs were almost always unrestrained. The infant was held in a “dangling” position in front of the parent and had much more range of motion available for their legs. The infants in the current study may have had more baseline distress from restraint, and this could cause higher pain scores than if baseline distress was absent. Cry, negative facial features and body movement can occur with infant distress or pain, and therefore distress cannot be distinguished from pain using the MBPS or other tools. VAS scores by observers may or may not exclude distress. The candidate noticed that some parents from the current study gave their infant low scores when the infant’s MBPS would be high and stated that their infant was “just tired” or similar.
Table 16: Pain scores compared with two other studies

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=60 Tactile stimulation</td>
<td>N=60 Standard care</td>
<td>N=60 Less painful injection first</td>
<td>N=56 Fast injection technique</td>
<td>N=57 Injection with aspiration</td>
</tr>
<tr>
<td>MBPS</td>
<td>7.6</td>
<td>7.2</td>
<td>6.3</td>
<td>3.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Cry duration (60 sec)</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Cried, number</td>
<td>52</td>
<td>47</td>
<td>41</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>Parent VAS (mm)</td>
<td>47</td>
<td>42</td>
<td>25</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>Researcher VAS (mm)</td>
<td>37</td>
<td>31</td>
<td>-</td>
<td>14</td>
<td>28</td>
</tr>
</tbody>
</table>

4.5 Recruitment of study participants

Parents opted to not participate in this study at a rate of 32%, which was high compared to two similar primary care immunization studies that did not have drug administration as part of the protocol. In the current study, clinic nurses made the initial contact with parent to discuss participation; if parents were agreeable, the candidate provided additional information and

‡‡‡‡‡‡ Pediacel® brand DTaP-IPV-Hib.
§§§§§§ Pentacel® brand of DTaP-IPV-Hib.
****** VAS scale 0 - 100 mm, 0 = no pain.
obtained written consent. In the other studies, the initial contact was made by the infant’s pediatrician.

Parent desire to have infants immunized by simultaneous injection was a major factor in refusal rate that was unique to this research environment. Well baby visits in Ontario, Canada had two immunization injections scheduled at 2, 4, 6 and 12 months during the time the study was occurring. About six months before the study began, nurses at the site started to perform tandem injections: two nurses, or a nurse and physician would each administer an injection in one of the infant’s legs (or child’s arms) at the same time. Their rationale for this procedure was that it would cause less pain and/or distress for the infants and children. Many nurses continued to offer tandem injections to infants at two months while the study was underway. Parent exposure to the tandem procedure at two months (which would include the nurse’s rationale and support for simultaneous injection) likely influenced their decision to refuse participation in this study that administered injections sequentially. Two studies have tested tandem versus sequential injection and failed to find a difference in the amount of pain experienced by participants.\(^91, 92\)

Another factor might have been waiting times prior to being seen in each of the offices: time was cited by a substantial number of parents, and this could have been time to complete the study but could have been related to how much time they had already spent waiting. No waiting time data were collected in the current study but another study found the average waiting time was 34 minutes (from arriving at office to being immunized).\(^93\) The site of the current study allotted 15 minutes for physician contact and 15 minutes for nurse contact at a well-baby visit, with immunization occurring at the end of the second 15 minute block. The candidate observed that sometimes infants were seen at the appointment time and others were seen later, but no attempt was made to capture the information systematically.

### 4.6 Strengths of study design

The strengths of this study include: randomizing participants, concealing treatment allocation to the recruiter, blinding the participants to group assignment and hypothesis, blinding the outcome assessor to the study intervention and hypothesis, using multiple clinicians, having an ethnically diverse population and using intent-to-treat analysis.
Several of these features improve internal validity, i.e. the likelihood that the results of the study are correct for this population. With randomization, a patient has an equal chance of being assigned to either treatment group. The result is that variables (both known and unknown) that could bias an outcome are more likely to be similar between groups.

Another feature of the study that improved internal validity was concealing the treatment assignment from the recruiter (the candidate). Studies have shown that when investigators are aware of what the next treatment assignment is, they may alter their recruitment behaviour (e.g. if a clinician thinks a patient’s sore throat is bacterial, the clinician might not recruit them for an antibiotic study if he or she knows they will be assigned to the placebo group), and the consequence is an exaggeration of treatment effect for the intervention group. It is important to note that this change in behaviour might be conscious or unconscious. In this study, the recruiter did not know which group the patient was assigned to until after consent had been obtained; therefore she could not influence the composition of each group.

Since the intervention in this study required participants to be trained to perform a specific behaviour, they were not blinded to their actions. However, the candidate did not disclose the research hypothesis or which behaviours were being studied – only that a combination of pain relieving strategies was being tested. Since parents were unaware if they were in a treatment or control group, they were less likely to bias their responses when asked about their infants’ pain and the procedures they had been asked to perform.

The primary outcome assessor who coded the MBPS (first rater mentioned earlier) was also blinded to the study hypothesis. In addition, she was initially blinded to the intervention being studied, although that may have become apparent after viewing a sufficient number of procedures (she reported at the end of coding that she was not certain what was being studied). Blinding the assessor makes it more likely the outcome is unbiased.

Several study strengths improve the external validity or generalizability of the study. Firstly, the design was a real-world scenario that included many different clinicians which mirrors actual practice where individual clinician habits may vary.

Another strong point of this study was ethnic diversity. Study participants included participants whose ethic origins were from Europe, Asia, Africa and native peoples of North and South
America. Although the issue of ethnicity and pain in infants requires further study, if differences exist, this group of participants was representative of the population of Canada and so the results are generalizable to them.

Additionally, the analysis for this study was done by intent-to-treat principles. All subjects were analyzed in the assigned group without regard to whether they received the intervention or not. The alternative is to use data from subjects who adhered to all aspects of the intervention (a per-protocol or on-treatment approach). The former is more reflective of what happens in the real world (patients are not consistently adherent to treatment) and so using this approach makes the results more generalizable. In addition, choosing which patients to include in the results (i.e. a per-protocol analysis) can remove the benefit of randomization and can introduce selection bias which may affect internal validity.

4.7 Study limitations

Some limitations to the study design should be considered when interpreting the results. In particular, the following must be considered: choice of parent and extent of training to provide the intervention, lack of placebo controlled blinding, and increased variability from lack of strict control on clinician behaviour.

Firstly, the results observed in this study can only be applied to parent-led tactile stimulation: a different result might be seen if clinicians performed tactile stimulation. Additionally, parent training was limited in this study and a different outcome might have occurred if more time were spent preparing parents to rub their infant’s leg during immunization; however, intensive training would be unlikely to occur in the real world, so generalizability would decrease.

A second consideration is that the study intervention was not truly blinded. This could bias results if clinicians treated individuals differently, if participants behaved differently or if the outcome assessor rated pain differently because of group assignment. The clinician, who was aware of the treatment assignment prior to the injections, could have treated the infant-parent dyad differently depending on group assignment; for example, she may have performed the injection differently in each group. Performing an injection is a motor skill that clinicians learn
during their training. Such skills become automatic and are done without thinking once learned. Therefore, it is unlikely that clinicians changed their practice based on group assignment. Sometimes a sham procedure is used in a study when a technique is being studied rather than a drug. This would not have blinded clinicians, and since the treatment being studied was not disclosed to participants, a sham procedure would have little impact on participants. It is possible that an unblinded outcome assessor could bias the results. The rater in this study was initially unaware of the intervention being studied and was not informed of the study hypothesis; therefore it is unlikely this occurred.

The “real world” scenario with multiple clinicians increases variability in pain response because of differences in clinician technique, infant position and restraint, waiting times, feeding status, and other factors not known. The extra variability might prevent the detection of an effect. However, increasing controls on the study would decrease the generalizability of the results.

4.8 Future research

Although this study found tactile stimulation administered by parents was not effective to reduce immunization pain in infants, studies in other populations that used clinician or investigator-led tactile stimulation found a reduction in pain from immunization and other injections; therefore, a study in infants to assess this intervention is warranted.

Separation of the measurement of pain and distress is not feasible with current tools and measures to reduce pain scores should consider reducing distress as well as pain. As noted earlier, operator-related factors may have contributed to differences in the scores, and these factors deserve some exploration. For example, a comparison of fast injection (e.g. < 2 seconds) versus typical speed (e.g. > 3 seconds) should be investigated for pain reduction. While a fast injection without aspiration was shown to be less painful than a regular-speed injection with aspiration, it is not known what portion of the pain was reduced from speed and what portion from lack of aspiration. Clinicians in the current study did not aspirate but injection speed was not as fast as that observed in the original research (as observed by the candidate but not systematically timed). This might have contributed to the higher pain scores observed in this
study (versus the two recent immunization studies)\textsuperscript{8,9} and should be investigated in a future study.

Infant restraint is another example of clinician variability that should be investigated. Infant position for immunization was very different between the current study and the two recent studies, with the latter two allowing relatively free movement of infant arms and legs during the entire process. The role of restraint warrants investigation.

Jet injectors, not currently available in Canada, are being used in the United States to administer lidocaine for local anaesthesia. The needle-free device forces a thin stream of drug into the skin at high pressure. Since topical local anaesthetics have been shown to reduce pain from immunization,\textsuperscript{56} the jet injector might offer an effective treatment that is faster to administer and could provide anaesthesia to a greater depth than currently available from topical local anesthetics. The pain from administration of local anaesthesia via a jet injector and injection of the vaccine should be assessed compared to the injection of the vaccine alone.

In addition, some vaccines are currently administered via needle-free jet injectors during mass vaccine campaigns. The pain from administration via this method should be compared with needle and syringe injection of the same vaccine to see if jet injector administration is less painful.
Chapter 5

5 Conclusion

Parent-led tactile stimulation was not effective to further reduce pain from immunization when added to a combination of pain relieving measures (oral sucrose, holding the infant, fast injection without aspiration). Parents found the procedures easy to do in the majority of cases but only half felt the infant benefited from their actions. No adverse effects were observed.

The results of this study are not consistent with other studies of tactile stimulation for injection pain, but none of the former studies had parents perform the intervention, and none were in infants.

The strategy cannot be recommended for use in infants; however, if a parent wishes to rub the skin, there is no evidence to recommend against the behaviour.

Clinicians may be better suited to deliver this intervention. Further research to investigate clinician-led tactile stimulation in this population is warranted.
References


13. Halperin BA, Halperin SA, McGrath P, Smith B, Houston T. Use of lidocaine-prilocaine patch to decrease intramuscular injection pain does not adversely affect the antibody


## Appendix A

### Appendix A: Modified Behavioral Pain Scale

<table>
<thead>
<tr>
<th>Observed behavior</th>
<th>Score (0-10)</th>
<th>Operational definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial expression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite positive expression.</td>
<td>0</td>
<td>Smiling.</td>
</tr>
<tr>
<td>Neutral expression.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Slightly negative expression: for example grimace.</td>
<td>2</td>
<td>Brow bulge, naso-labial furrow.</td>
</tr>
<tr>
<td>Definite negative expression: i.e. furrowed brows, eyes closed tightly</td>
<td>3</td>
<td>Brow bulge, naso-labial furrow, eyes closed tight, open lips with or without reddened face.</td>
</tr>
<tr>
<td><strong>Cry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laughing or giggling.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Not crying.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moaning, quiet vocalizing, gentle or whimpering cry.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Full lunged cry or sobbing.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Full lunged cry, more than baseline cry.</td>
<td>4</td>
<td>To be scored only if infant is crying during baseline.</td>
</tr>
<tr>
<td><strong>Movements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual movements/activity, or resting/relaxed.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial movement or attempt to avoid pain by withdrawing the limb where the puncture is done.</td>
<td>2</td>
<td>Squirming, arching, limb tensing/clenching.</td>
</tr>
<tr>
<td>Agitation with complex movements involving the head, torso or the other limbs, or rigidity.</td>
<td>3</td>
<td>Generalized limb and/or body movements, or rigidity.</td>
</tr>
</tbody>
</table>
Appendix B

Appendix B: Vaccination pain fact sheets

Vaccination Pain Fact Sheet

What YOU as a Parent CAN DO

Vaccinations given with a needle may cause pain. During the injection, your actions and words can influence your infant’s reaction. Infants often look to their parents to understand how to act and feel. Read on and find out what you should not say, what you should say and what you should do to help your infant cope.

WHAT NOT TO SAY:
- DON’T reassure: “It’ll be over soon and you’ll be ok.”
- DON’T apologize: “I’m sorry you have to go through this.”
- DON’T empathize: “I know it hurts.”

Scientists suggest that one reason these types of statements don’t work is because parents only use them when they are worried that their infant is going to be upset at something distressing.

WHAT TO SAY:
- DO use your normal voice, smile and be cool; your infant will feel that everything is OK. Talk about things that can help distract your infant so their mind focuses on something else. Some parents report it helps calm them down too!

WHAT TO DO:
- DO hold your infant close: Holding, cuddling, or hugging an infant provides comfort during the procedure. Have your infant sit up-right in your lap or in a bear hug during the injection.
- DO rub the skin: Gently rub the skin near the injection site right before, during and for a short time after the vaccination. You can choose how much pressure is best for your infant. Pick a pattern of rubbing that is easy for you (e.g. up and down, side-to-side, circles).

Remember:
BE COOL
HOLD CLOSE
GENTLY RUB
Vaccination Pain Fact Sheet

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Remember:
BE COOL
HOLD CLOSE
Appendix C

Appendix C: Consent form

Title of Research Project:
Reducing Pain in four- to six-month old infants undergoing immunization using a multi-modal approach

Investigator(s):
Principal Investigator:
Ms. Janet Probst, RN (416) 323-6400, Women’s College Hospital

Co-Investigators:
Dr Karen Wong, MD (416) 323-6400, Women’s College Hospital
Dr Mary-Ellen Hogan, PharmD (416) 951-8059, University of Toronto
Dr Rebecca Pillai Riddell, PhD (416)-736-2100, York University
Dr. Joel Katz, PhD (416) 736-2100, York University
Dr. Anna Taddio, PhD (416) 978-8822, University of Toronto

Sponsor:
Canadian Institutes of Health Research (CIHR)

Introduction:
Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study staff to explain any words you don’t understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Purpose of the Research:
Infants experience pain from immunization injections. At present, there are several non-drug strategies that may help to reduce pain. However, they are not used routinely, perhaps because they are inconvenient or do not work that well. In this study, we will test some non-drug strategies for reducing immunization pain in infants and ask parents if they think the methods are convenient.
**Description of the Research:**
Infants who participate in this study are having their routine 4 or 6 month immunization injection. In addition to usual care, infants who participate will receive different strategies to reduce pain. Parents will be given an information sheet that contains information about ways to reduce pain, including: infant positioning and parental behaviours to use. Half of the parents will try one combination of techniques and the other half will try another combination and we will compare their pain responses. In addition, all infants will get sugar water (about ½ teaspoonful) in the mouth before immunization and the vaccine will be injected quickly.

The immunization procedure will be videotaped. Parents will be asked to rate their infant’s pain and to comment on the pain management techniques they used. Videotapes will be viewed later by a research assistant that does not know the identity of infants to score their pain.

Usual care for infants receiving immunization does not always include sugar water, fast injection technique or instructions for parents about infant positioning and behaviours to use during immunization.

This study is taking place at the Family Practice Health Centre at Women’s College Hospital. A total of 120 infants will be enrolled in this study. It is expected that the entire study will take about one and a half years to complete. Each infant can participate in the study one time.

Infant health record charts will be reviewed as part of this study to gather information about the birth characteristics of participants (such as weight, gestational age at birth, sex, clinical conditions, and medications used).

**Potential Harms:**
Sugar water is considered safe for infants to eat. Other interventions that may be used (holding infants, rubbing skin, providing distraction) do not interfere with the procedure and are not linked to any adverse effects.

**Potential Discomforts or Inconvenience:**
Some extra time will be required to answer questions and videotape the immunization procedure. This may mean that your visit lasts up to an hour rather than the usual amount of time.

**Potential Benefits:**
Your child may benefit from a less painful immunization injection because she or he will receive pain relieving interventions during immunization.

Infants in the future may benefit from the results of this study because we will know more about how to reduce pain during immunization.

**Alternatives to participation:**
Your infant will receive the standard method of immunization without videorecording, as per the current standard of care at your doctor’s office. This may or may not include sugar water or other pain-relieving interventions.
**Confidentiality:**
We will respect your privacy. No information about you or your child will be given to anyone or be published without your permission, unless the law requires us to do this. For example, the law requires us to give information about you or your child if a child has been abused, if you or your child has an illness that could spread to others, if you or someone else talks about suicide (killing themselves), or if the court orders us to give them the study papers.

Women’s College Hospital Research Ethics Board members may see your child’s health record to check on the study.

By signing this consent form, you agree to let these people look at your child’s records. We will put a copy of this research consent form in your child’s patient health records. We will give you a copy for your files.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study, the data will be kept as long as required and then destroyed as required by Women’s College Hospital policy. Published study results will not reveal your identity.

**Reimbursement:**
There is no reimbursement for this study.

**Participation:**
If you choose to let your child take part in this study you can take your child out of the study at any time. The care your child gets at this office will not be affected in any way by whether your child takes part in this study.

Your signing this consent form does not interfere with your legal rights in any way. The study staff, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

**Sponsorship:**
This study is being sponsored by The Canadian Institutes of Health Research (CIHR) through a New Investigator grant to Dr. A. Taddio.

**Conflict of Interest:**
The research team members have no conflict of interest to declare.
Consent:

By signing this form, I agree that:

1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.
3) I know what I could do instead of having my child take part in this study. I understand that I have the right to refuse to let my child take part in the study. I also have the right to take my child out of the study at any time. My decision about my child taking part in the study will not affect my child’s health care at Women’s College Hospital.
4) I am free now, and in the future, to ask questions about the study.
5) I have been told that my child’s medical records will be kept private except as described to me.
6) I understand that no information about my child will be given to anyone or be published without first asking my permission.
7) I have read and understood pages 1 to 5 of this consent form. I agree, or consent, that my child___________________ may take part in this study.

Printed Name of Parent/Legal Guardian Parent/Legal Guardian’s signature & date

Printed Name of person who explained consent Signature & date

Printed Witness’ name (if the parent/legal guardian does not read English) Witness’ signature & date

If you have any questions about this study, please call Ms. Janet Probst at (416) 323 6060.

If you have questions about your rights as a subject in a study or injuries during a study, please call Dianna Raymond-Watts, Manager of the Research Ethics Board at (416)-351-2535.
While I do not consent to have my child participate in this study, I consent to providing information to investigators about myself and my family (infant birth date, weight, sex, and reason for refusal). This information is being used to ensure that the characteristics of participating infants do not differ from non-participating infants.

______________________________________________  __________________________________________
Printed Name of Parent/Legal Guardian  Parent/Legal Guardian’s signature & date

______________________________________________  __________________________________________
Printed Name of person who explained consent  Signature & date

______________________________________________  __________________________________________
Printed Witness’ name (if the parent/legal guardian does not read English)  Witness’ signature & date
Appendix D

Appendix D: Parent survey

Reducing Pain in four- to six-month old infants undergoing immunization using a multi-modal approach

Parent survey

1. Was the Fact Sheet easy to understand? (please circle number)

<table>
<thead>
<tr>
<th></th>
<th>Very easy</th>
<th>Somewhat easy</th>
<th>Neutral</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. How easy was it to do everything the Fact Sheet suggested?

<table>
<thead>
<tr>
<th></th>
<th>Very easy</th>
<th>Somewhat easy</th>
<th>Neutral</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

a) Please explain your response:

___________________________________________________________________________
___________________________________________________________________________

3. Do you think your infant had a less painful experience as a result of what you did?

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

a) Please explain your response:

___________________________________________________________________________
___________________________________________________________________________

4. Will you use the information you learned from the Fact Sheet in future immunizations?

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

a) Please explain your response:

___________________________________________________________________________
___________________________________________________________________________

Circle **ALL** that you did for this procedure:

1 = Sugar water  
2 = Held infant  
3 = Stayed cool (please explain)  
4 = Rubbed skin  
5 = Other:

Circle **ALL** that you will do in the future:

1 = Sugar water  
2 = Hold infant  
3 = Stay cool (please explain)  
4 = Rub skin  
5 = Other:

THANK YOU FOR YOUR PARTICIPATION
Appendix E

Appendix E: Data form

Reducing pain in four- to six-month old infants undergoing immunization using a multi-modal approach

◆ Use a ball point pen and press firmly

Observer’s Initials:_______________________

Return To:
Dr. Anna Taddio
Leslie Dan Faculty of Pharmacy
University of Toronto
144 College Street, Toronto, ON
M5S 3M2 Tel. 416-978-8822

DOCUMENTATION OF INFANT ELIGIBILITY
STEP A: INCLUSION CRITERIA

Infant MUST present with ALL of the following:

No  Yes

☐  ☐  Healthy infant coming in for 4 or 6 month routine immunization

If NO to ANY Inclusion Criterion, infant is NOT ELIGIBLE for randomization.

STEP B: EXCLUSION CRITERIA

Infant MUST have NONE of the following:

No  Yes

☐  ☐  1. Impaired neurological development.

☐  ☐  2. History of seizure.

☐  ☐  3. Use of sedatives or narcotics in preceding 24 hours.

☐  ☐  4. Infant or parent is unable to use the assessment tools in the study.

☐  ☐  5. Prior participation in this trial.

If YES to ANY Exclusion Criterion, infant is NOT ELIGIBLE for randomization.

If infant meets all Inclusion criteria and has no Exclusion criteria present patient is eligible.

Please confirm if written consent has been provided:  ☐  No  ☐  Yes

Investigator’s Signature:  ___________________________  Date:  ________ ______ ______
**FAMILY DATA**

**DEMOGRAPHICS**

**Ethnicity:**
- [ ] Caucasian
  Origins in Europe, Middle East, North Africa (Arabic origins), Western Russia including Afghanistan and South Russia) and Hispanics of European origin.
- [ ] Afro-American or African
  Origins in any of the original peoples of Africa.
- [ ] Asian
  Origins in the Indian sub-continent (eg. India, Pakistan, Bangladesh and Sri Lanka), OR in the Far East and Southeast Asia (eg. China, Japan, Korea, Philippines, Thailand, Eastern Russia and Samoa).
- [ ] Other - specify
  ____________________________
  Includes origins not represented above, eg. Inuit, Maori, Australian Aborigine, North & South American Native Peoples, Hispanics of Caribbean, Central & South American origin, and Pacific Islanders.

**Family Arrangement:**
- [ ] Single-parent family
- [ ] Two-parent family

**Parent bringing child in for appointment Parents**
- [ ] Father
- [ ] Mother
- [ ] Both
- [ ] Other: ____________________________

**Number of siblings at home:** _____________
INFANT DATA

Baseline Data:

Baby is attending office for:  □ 4 month immunization  □ 6 month immunization

Date of Birth:  __ __ __  __ __ __  __

Was infant born prematurely?  □ YES  □ NO

What was the infant’s gestational age at birth:  __ __ __  __ __

Sex:  □ Female  □ Male

Any medical conditions?  □ YES  □ NO

If yes, list them: ____________________________________________________________

History of painful procedures

Was baby born by vaginal delivery?  □ YES  □ NO

Were forceps used?  □ YES  □ NO  Was vacuum used?  □ YES  □ NO

If male, is baby circumcised?  □ YES  □ NO  Not applicable (baby is female)

Has infant been hospitalized since birth?  □ YES  □ NO

Was infant in hospital for greater than one week at birth?  □ YES  □ NO

If yes to either of hospitalization questions, describe circumstances (use back of sheet if more space is required):

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

Previous immunization  DTaP-IPV-Hib (dd-mm-yy)  PCV (dd-mm-yy)

<table>
<thead>
<tr>
<th>Previous immunization</th>
<th>DTaP-IPV-Hib (dd-mm-yy)</th>
<th>PCV (dd-mm-yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 month</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(□ other immunization: specify:________________________________________)
INFANT DATA

On day of procedure

Current weight (specify kg or lb): __________________________

Is baby currently being breastfed?  □  YES  □  NO  □  Partial:____________________

Baby’s last nap before immunization

<table>
<thead>
<tr>
<th>Date (dd/mm/yyyy)</th>
<th>Start time (24h)</th>
<th>Duration (hr, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Last feeding before immunization

<table>
<thead>
<tr>
<th>Date (dd/mm/yyyy)</th>
<th>End time (24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was infant given ibuprofen (Advil/Motrin) or acetaminophen (Tylenol/Tempra) before the appointment for immunization?  □  YES  □  NO

If yes, specify drug, dose given and date and time of administration:

____________________________________________________________________________________

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**PROCEDURE**

Infant randomized to rubbing:  
☐ YES  ☐ NO

Has parent been given Fact Sheet?  
☐ YES  ☐ NO

Specify version of Fact Sheet:  
☐ R  ☐ X

### Sucrose administration

<table>
<thead>
<tr>
<th>Start time (24h)</th>
<th>End time (24h)</th>
<th>Given by</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 minutes before first injection (DTaP-IPV-Hib)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baby held by:  
☐ Parent  ☐ Nurse  ☐ Other  
(specify): ______________________________________

Specify how held: ______________________________________

Rubbing performed by parent:  
☐ YES  ☐ NO

### Other Non-Pharmacological Interventions during immunization

Pacifier:  
☐ No  ☐ Yes  
Comments: ______________________________________

Toy:  
☐ No  ☐ Yes  
Comments: ______________________________________

Other:  
☐ No  ☐ Yes  
Comments: ______________________________________

<table>
<thead>
<tr>
<th>Injection</th>
<th>Time (24h)</th>
<th>Site (e.g. right leg)</th>
<th>Successful</th>
</tr>
</thead>
<tbody>
<tr>
<td>First (DTaP-IPV-Hib)</td>
<td></td>
<td></td>
<td>Y / N</td>
</tr>
<tr>
<td>Second (PCV)</td>
<td></td>
<td></td>
<td>Y / N</td>
</tr>
</tbody>
</table>

*If possible, DO NOT perform procedures on crying infants.*
Injection 1: Needle size: 25 gauge needle, 25 mm; Other - Specify gauge, specify length mm
Injection 2: Needle size: 25 gauge needle, 25 mm; Other - Specify gauge, specify length mm
Brand of DTaP-IPV-Hib: Pediacel, Pentacel, Other - Specify: 
Lot number and expiry of DTaP-IPV-Hib: LOT EXP:
Brand of PCV: Prevnar, Other - Specify: 
Lot number and expiry of PCV: LOT EXP:
Clinician name: # Years of practice:
Clinician type: Nurse, Nurse practitioner, FP/GP, Other - Comments
Clinician time of experience with fast injection technique: years; months.
Additional notes:
WITHDRAWAL OF PATIENT FROM STUDY

Date (dd/mm/yr):_____________________

REASON(S) FOR WITHDRAWAL (check all that apply):

☐ Adverse event, please specify ____________________________________________

☐ Parental refusal to continue with study, please specify _______________________

☐ Major deviation from protocol, please specify ________________________________

☐ Other, please specify ____________________________________________________
Appendix F

Appendix F: Supplemental MAISD data

Table F1: Incidence of MAISD components for parent holding baby

<table>
<thead>
<tr>
<th>Item</th>
<th>Before injection</th>
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<th></th>
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<td>Standard</td>
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<td>Standard</td>
</tr>
<tr>
<td></td>
<td>stimulation</td>
<td>care</td>
<td>stimulation</td>
<td>care</td>
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<td>n=60</td>
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<td>2</td>
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<td>3</td>
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</tr>
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<td>Item</td>
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<td></td>
<td>After injection</td>
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<td>-----------------</td>
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</tr>
<tr>
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Table F2: Incidence of MAISD components for second parent in room

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<td>n=9</td>
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<td>Rub leg, injection 2</td>
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<td>Item</td>
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<td>After injection</td>
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<td>------------------</td>
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<tr>
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### Table F3: Incidence of MAISD components for clinician

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<td>n=60</td>
</tr>
<tr>
<td>Distraction (verbal), injection 1</td>
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</tr>
<tr>
<td>Distraction (verbal), injection 2</td>
<td>2</td>
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<tr>
<td>Distraction (non-verbal), injection 1</td>
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</tr>
<tr>
<td>Distraction (non-verbal), injection 2</td>
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</tr>
<tr>
<td>Verbal reassurance, injection 1</td>
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<td>2</td>
</tr>
<tr>
<td>Verbal reassurance, injection 2</td>
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<td>3</td>
</tr>
<tr>
<td>Procedural talk, injection 1</td>
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</tr>
<tr>
<td>Procedural talk, injection 2</td>
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<td>14</td>
</tr>
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</table>
Appendix G

Appendix G: Visual analog scale

VISUAL ANALOG SCALE
ASSESSMENT OF PAIN

Assessment is for:  □ Injection 1:  □ Injection 2
Assessment is for:  □ Pre-injection:  □ Post-injection

Rater:  □ Mother  □ Father  □ Research assistant  □ Other
Specify:____________________

Name of research assistant:  ______________________________________________________

Date of assessment  ❌  ❌  ❌  Time of assessment:  ❌  ❌  ❌
   dd   mm   yr (24 hour clock)

No pain  ___________________________ Worst pain ever