

# **Proceedings of the Workshop**

## ***Conquering Pain: The Hidden Cost of Immunization***

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## **Main Messages**

### **Pain during Routine Childhood Immunization is a Problem!**

- Immunization is a global priority for the prevention of morbidity and mortality caused by infectious diseases. The procedure of administering vaccines, however, involves a needle puncture, which is painful. Although research has demonstrated various effective ways of reducing pain during needle punctures, they are not being used in clinical practice.

### **Workshop Attendees and Objectives:**

- Researchers, vaccine experts, healthcare workers, educators, government officials, parents, pharmaceutical company representatives, and media representatives convened for a 1-day meeting to discuss the research knowledge related to: 1) the importance of pain management in children, and 2) the effectiveness of analgesic interventions; and 3) to make recommendations that will lead to improvements in pain management practices.

### **What We Know about Pain and Immunization in Children:**

- Pain caused from injection of vaccines is important to treat:
  - ⇒ Infants and children feel pain during injections of vaccines
  - ⇒ Parents are distressed by the pain and may avoid or delay immunization due to pain; parents are willing to pay to reduce pain in their children
  - ⇒ Experience with needle puncture pain in childhood may lead to anxiety before future procedures, more pain at future procedures, and needle phobia
- Effective ways to reduce pain during injection of vaccines:
  - ⇒ Analgesic drugs (topical local anaesthetics, vapocoolants), sugar water (young infants)
  - ⇒ Cognitive-behavioural approaches (distraction, nurse coaching, coping skills, deep breathing, demonstration and parent participation)
  - ⇒ Injection techniques including: quick injections without aspiration, Priorix<sup>®</sup> rather than MMR-II<sup>®</sup>, intramuscular injection at a 90 degree angle, antero-lateral thigh for injection in infants < 12 months old and deltoid muscle for injection in infants > 1 year old, administration of the least painful vaccine first.

### **Conclusions and Recommendations:**

- Parents need to be better informed about the impact of routine immunization-related pain in children. To this end, pamphlets for parents will be developed and parents are encouraged to talk to their healthcare professional about their options.
- Children need to be better informed on what they can expect during routine immunization. Members of the panel will write a children's book to help educate children.
- Healthcare professionals need to be better informed about the impact of immunization and ways of minimizing the pain. National practice guidelines need to be developed and governing bodies need to ensure that these guidelines are disseminated and adhered to. Development of national guidelines and educational initiatives will be spearheaded by panel members and workshop participants.
- Findings and conclusions from this workshop need to be shared with others and this will take the form of a white paper/proceedings and publications by panel members.

## 3-Page Executive Summary

Immunization is a global priority for the prevention of morbidity and mortality caused by infectious diseases. The procedure of administering vaccines, however, involves a needle puncture, which is painful. **Pain during immunization is a significant burden for children and their families and negatively impacts on their future healthcare experiences.** Although current research demonstrates that pain can be reduced using pharmacological, psychological and injection-administration techniques, these strategies are not widely used in the community. A knowledge translation (KT) intervention is required to improve pain management practices.

**In response to this need, a workshop was held in Toronto on January 28, 2008.** The title of the workshop was ‘**Conquering Pain: The Hidden Cost of Immunization.**’

The event was sponsored by the **Canadian Institutes of Health Research (CIHR), The SickKids Foundation,** and the **Leslie Dan Faculty of Pharmacy, University of Toronto.**

Attendees included; researchers, vaccine experts, healthcare workers, educators, government officials, parents, pharmaceutical company representatives, and media representatives.

### **The Goals of workshop were to:**

- 1) Build a network of invested stakeholders,
- 2) Examine the evidence for the importance of pain management during routine childhood immunization and the effectiveness of different analgesic strategies,
- 3) Identify barriers to pain management, and
- 4) Identify interventions that reduce pain, and strategies for their implementation.

Plenary sessions by experts offered overviews of the current guidelines for childhood immunization in Canada, sequelae of untreated procedural pain in childhood, current analgesic practices during childhood immunization, barriers to pain management in children, and the clinical efficacy for various pharmacological, psychological and vaccine-administration techniques.

**It was concluded that:**

- Infants and children feel pain during injection of vaccines. Experience with needle puncture pain in childhood may lead to anxiety before future procedures, more pain at future procedures, and needle phobia.
- Parents are distressed by the pain and may avoid or delay future immunization in their child(ren). Parents are willing to pay to reduce pain during immunization.
- Barriers to optimal pain management include: lack of knowledge of the significance of pain for children and their families and of the willingness of parents to pay for analgesics to reduce pain in their children; lack of knowledge of effective analgesic strategies and how to incorporate them in practice; difficulty educating and changing behaviours of healthcare workers in order to minimize pain during immunization.
- Gaps in research are a problem. In particular, there is a scarcity of information in clinical trials on the pain caused from new vaccines and modulating impacts of different formulations and local anaesthetics; lack of knowledge on how the physical environment (setting) impacts on pain during immunization, and minimal knowledge on pain management in the hours to days post-vaccine injection.
- Based on the research reviewed, the following strategies reduce pain during injection of vaccines in infants and children:
  - Analgesics (topical local anesthetics, vapocoolants) and sugar water (in young infants)
  - Cognitive-behavioural approaches (distraction, nurse coaching, coping skills, deep breathing, demonstration and parent participation)
  - Injection techniques including; quick injection without aspiration, Priorix<sup>®</sup> rather than MMR-II<sup>®</sup>, intramuscular injection at a 90 degree angle, antero-lateral thigh for injection in infants < 12 months old and deltoid muscle for injection in infants > 1 year old, administration of the least painful vaccine first.
- Although pain has typically been a routine part of immunization, it does not need to be. There is sufficient evidence for implementable strategies to significantly impact on the immunization experience for children and their families. Pain relief is a basic human right. It was agreed that children should not suffer needlessly and that we can make a difference.

**Key target groups that were identified for dissemination of knowledge include:**

parents and children; nurses, physicians (pediatricians and family practice), pharmacists, and governmental officials (ministry and public health).

**The group concluded with actionable plans to advance pain management during routine childhood immunization.**

These actionable plans include:

- 1) Development of a steering committee to oversee future activities;
- 2) Application for funding for future activities;
- 3) Publication of a summary of the proceedings;
- 4) Publication of systematic reviews;
- 5) Development of national guidelines for pain management; and
- 6) Development of dissemination strategies (i.e., educational materials such books, videos, pamphlets).

## **Introduction**

The workshop was held on January 28, 2008 at the Leslie Dan Faculty of Pharmacy, University of Toronto. The event was sponsored by the Canadian Institutes of Health Research, The SickKids Foundation, and the Leslie Dan Faculty of Pharmacy, University of Toronto.

The workshop was attended by 35 individuals (27 invited guests, 7 plenary speakers, and 1 facilitator). In the morning, presentations were made by faculty on the following topics: current guidelines for immunization in Canada; sequelae of untreated pain in childhood; current analgesic practices; barriers to pain management in children; and the clinical efficacy for various pharmacological, psychological and vaccine-administration strategies. The plenary sessions were followed by group discussions in the afternoon by faculty and participants aimed at identifying areas where there was sufficient evidence to recommend changes in practice. In addition, gaps in knowledge and barriers to optimal pain management were identified and discussed. The group identified key stakeholder groups and potential interventions. Next steps were prioritized and an action plan was developed for future work.

## **Welcome and Opening Remarks**

Dr. Anna Taddio, Associate Professor, Leslie Dan Faculty of Pharmacy, and Adjunct Scientist, The Hospital for Sick Children, and Project Leader for this workshop, gave opening remarks and thanked everyone for coming to the meeting. She stated that for the first time, all of the stakeholders involved in childhood immunization were together in a room talking about pain. She stated that the World Health Organization estimates that 100 million children receive immunizations worldwide every year, and that children have the right to internationally accepted, evidence based pain management during medical procedures. However, they are not getting it. The problem of pain during immunization is ubiquitous and needs to be addressed. Dr. Taddio reviewed the International Association for the Study of Pain (IASP) definition of pain, which states that ‘pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.’ Furthermore, pain is subjective and shaped by early life experiences. Immunization is part of early life experience with pain, and can therefore affect future interpretations of pain. She stated that it is our moral obligation to reduce pain in infants and children, especially when it is inflicted by us. Reducing a child’s pain not only benefits the child, but helps healthcare workers and parents as well, because they are distressed when pain is inflicted on children.

Dr. Taddio outlined the objectives of the workshop, which were to: 1) build a network of invested stakeholders, 2) understand research evidence and identify needs for future research, 3) identify barriers to pain management, and 4) identify interventions that reduce pain, and strategies for their implementation.

Dr. Taddio then introduced the plenary speakers (Dr. Scott Halperin, Dr. Christine Chambers, Dr. Vibhuti Shah, Dr. Donna Lockett, Dr. Moshe Ipp, and Dr. Michael Rieder) and the workshop facilitator (Dr. David Shute, Greenfield Health, Portland, Oregon, U.S.).

Dr. David Shute stated that the challenge for management of immunization pain is translating knowledge into practice. He also stated that the value of the meeting would come from dialogue amongst the participants, which were very diverse. He asked the participants to introduce themselves, and then guided the panel and participants through the morning plenary sessions and afternoon open discussions/workshops.



## **Plenary Sessions**

### **1. Update on Vaccine Programs in Canada**

Dr. Scott Halperin, Vaccinologist and Infectious Diseases expert at Dalhousie University, reviewed current immunization guidelines in Canada. He stated that there were many different vaccine schedules across different countries and that they are developed according to the epidemiology of diseases affecting each region and the age in which the diseases occur. The vaccines used depend on their characteristics, economic impact and political priorities. There are many vaccine programs across Canada, although in Dr. Halperin's opinion, there could probably be just one. Dr. Halperin named 17 antigens in national programs and stated that all but 3 of them were routinely used. The paediatric vaccination schedule in Canada varies by province.

Dr. Halperin stated that what vaccinologists have been doing to help with the reduction of pain is to try to give as many vaccines as possible as a single injection. This improves compliance, record-keeping, and results in fewer doctor visits and costs, and improved comfort and patient satisfaction. On the other hand, it reduces vaccine program flexibility, because individual vaccines may not be administered. In addition, it may increase the cost of the product and decrease the frequency of physician contacts with patients. Dr. Halperin stated that the adverse events from combination vaccines are at worst additive, but most often the adverse events associated with combination vaccines are less than the sum of the constituents.

Dr. Halperin reviewed the different ways vaccines can be administered. By injection, these include: intramuscular, subcutaneous or intradermal. There are also oral vaccines available, including poliovirus, rotavirus, typhoid, and cholera. Nasal influenza vaccine is available in the US. Other nasal vaccines are being developed. In addition, there is research on the development of vaccines that may be eaten, and transcutaneous patches (not used routinely in Canada).

Dr. Halperin stated that injectable vaccines are painful, and the pain can be related to the adjuvant, route of administration, antigen, immune response, or the composition of the vaccine (such as the pH). He suggested that all vaccines will not eventually be needle free because the cost of development of a new vaccine in the absence of disease pressure is too great. The management of pain for the old vaccines will be more important than developing new vaccines.

Dr. Halperin ended his presentation by stating that some vaccines were clearly more painful than others and that to date, decreasing pain to minimal levels was not a priority during the drug development phase.

## **2. The Hidden Cost of Immunization**

Dr. Donna Lockett, Knowledge Translation Broker, The Hospital for Sick Children, and psychotherapist, ClearSolutions, outlined the harms of pain in children. She opened her session with a request for the participants to close their eyes and imagine their response to a needle puncture. The participants reviewed their feelings, which included tension, anxiety and anticipation. Then Dr. Lockett displayed a video clip of a 3-year old child that required a needle procedure. The child became distressed when he became aware that he was going to be poked and tried to escape. He was subsequently restrained by several adults and became severely distressed. His distress was further elevated during the actual procedure.

Dr. Lockett explained that trauma is a heightened response of stress, and that it is in the nervous system. She explained the ‘fight or flight’ response is present early in evolution (in the reptilian brain). She further described that a traumatic event is either a single or repeated event that happens ‘too fast,’ ‘too soon’ and ‘too much’ and results in a breach in protective barriers against stimulation, leading to a loss of resilience in the nervous system. Immunization may potentially be a source of trauma if the child is not sufficiently prepared. There is a lot of energy stored up in the nervous system and when there is stress, this energy is released. In nature, there is a flight, fight, or freeze response; however, we don’t have these options in society and are unable to release the energy. The effects of trauma may last a long time, sometimes a lifetime.

Dr. Lockett explained that many of the clients in her practice demonstrated reactions that could be traced to when they were as young as 5 years old. As newborns, infants have a nervous system is sufficiently mature to feel pain. What is immature at birth is the ability to dampen incoming pain signals, so newborns may actually feel ‘more pain’ after the same stimulus when compared to adults. Medical procedures are associated with child factors (immature cognitive development, inability to understand the value of the procedure, and memory of negative prior procedures), procedural factors (chaotic environment, inadequate treatment of pain and distress, lack of control), and memory factors (fragmented traumatic memories result in distorted exaggerated memories).

Dr. Lockett quoted studies demonstrating the long-term consequences of untreated pain in infants and children including: anticipatory fear (demonstrating distress before pain is inflicted due to anticipation of pain); hyperalgesia (an increased response to a stimulus which is normally painful) even without fear; and an increase in the dose of pain reliever needed to reduce pain for future procedures. In a previous study, pain during 4 and 6-month immunization was higher for male infants that were circumcised compared to male infants that were not circumcised demonstrating that past pain experience sets us up to react to pain differently in the future. In addition, studies have demonstrated that past experience with pain in preterm infants may be associated with somatization in childhood. Fear of needles has been demonstrated to lead to healthcare avoidance, including reduced immunization compliance, poor diabetes management, missed/avoided dental care, avoidance of blood donation and avoidance of other medical situations.

In approximately 10% of the population, the fear of needles is so great that they are referred to as 'needle phobic'. Needle phobia occurs in susceptible individuals after a negative experience involving a needle. Dr. Lockett described a child that developed a needle phobia which led to a fear of bees, then generalized to a fear of all insects, and in turn, to a fear of the outdoors. This snowball effect led to social isolation and poor development.

Dr. Lockett stated that repeated pain in animals and children were associated with behavioural changes and post-traumatic stress disorder, but that infants that had received adequate analgesia were not affected. Dr. Lockett then ended her presentation with some references for the participants.

### **3. Current Analgesic Practices: Results of a Pain Audit**

Dr. Anna Taddio reviewed the results of a study of current analgesic practices during routine immunization in the Greater Toronto Area (GTA) in 2007. The study examined what mothers and pediatricians were doing to manage pain in children undergoing immunization and some of the barriers to pain management. Dr. Taddio specified that the primary focus was management of pain from the needle poke (that is, vaccine injection) and that her research team examined the different ways that this pain could be diminished: 1) by using medications such as topical local anesthetic creams or oral analgesics; 2) by using various injection techniques; 3) by using psychological interventions (such as distraction).

When 200 mothers were asked what they did to manage needle puncture pain in their 274 children, they said they gave topical local anesthetics to 4 (1%) of them. Almost a quarter of children, however, received oral analgesics. Dr. Taddio commented that local anesthetics have been proven to reduce needle puncture pain during routine immunization while oral analgesics have not. The majority of mothers held their children during immunization. However, it is not known whether the child was restrained rather than supported or comforted, which might have increased the pain experience for the child. The mothers used distraction methods, but very few used other methods such as feeding, pacifiers and sweeteners. Sweeteners such as sugar water have analgesic properties in young infants.

When pediatricians were asked what they did to reduce pain, almost 50% said they injected the vaccine quickly. Conversely, almost 20% injected the vaccine slowly. One third of physicians injected the vaccine without aspirating; aspirating adds a step, increases the duration of the procedure and makes it hurt more. Dr. Taddio summarized by saying that pain is not well managed by vaccinators.

Dr. Taddio then reviewed why mothers don't use analgesics in their children. The main reasons were that either their physicians did not tell them to use analgesics or that they were unfamiliar with them. Others were concerned about the possibility of side effects and did not want to compound worrying about the side effects of the vaccine with the side effects of the analgesic. A smaller number of mothers said they had not used analgesics in the past. Pediatricians most commonly stated that they didn't use analgesics because it was not their usual practice, or because parents did not ask about them. Physicians also stated that using analgesics would add time to the visit and cost too much; both of these latter concerns are not substantiated by the medical literature and local hospital outpatient clinic practices. Parents can be shown how to apply local anesthetics at home and demonstrate a willingness to pay for analgesics.

There are clearly barriers to optimal pain management. The biggest gap is the knowledge gap: parents do not know that pain management strategies are available and how to implement them. Parents also have concerns about the side effects of drugs. Physicians believe that the drugs are not feasible to use and there is a prevailing attitude that managing pain is not important. Parents have indicated in several studies of immunization pain that they would pay to reduce pain in their children, by about \$10-25; interestingly, younger and parents of lower income have been shown to be willing to pay more. Pain is the worst part of medical treatment and the needle is the most

distressing object in the hospital. At SickKids, pain is a priority and there are hospital-wide initiatives underway to improve pain management. Pain causes adverse long-term effects- fears of the needle affect future lifestyle and healthcare decisions. Dr. Taddio said that studies demonstrated that parents can and will use local anesthetics. Dr. Taddio then showed a video clip of the currently marketed local anesthetics and a demonstration of the application of one of them onto the arm of a 6-year old prior to immunization.

Dr. Taddio stated that the goal of pain management is elimination of pain, but that a reduction in pain was also important. Dr. Taddio stated that it is not unusual to combine drugs in order to optimally manage a condition. For example, in patients with hypertension, a single drug often is not enough to bring down the blood pressure to normal range and multiple drugs need to be used. She stated that pain was similar- multiple analgesic interventions might be needed for optimal results.

Dr. Taddio stated that pain management is an under achieved goal of modern medicine and that this is partly due to societal beliefs about pain (lack of importance of pain). Parents may not ask for pain relief in their children because they do not want to appear as complainers. In addition, pain is a central part of many religions and it is believed that enduring pain is needed for redemption. This leads adults to impose pain on children, and themselves. But for children, pain is more traumatic due to the inability to understand it and cope with it. Dr. Taddio ended her session by saying that it wasn't long ago when newborn male circumcision was routinely performed without analgesia until we demonstrated that there were long-term consequences of it, and similarly, we need to treat immunization pain.

#### **4. Systematic review of Analgesic interventions for Reducing Pain during Immunization**

Dr. Vibhuti Shah, Neonatologist and Epidemiologist, Mount Sinai Hospital, reviewed the evidence for four classes of pain relievers: topical local anaesthetics, sweetening agents (sugar water), coolants, and oral analgesics.

She stated that the most extensively studied analgesics are the topical local anaesthetics. They work by preventing pain impulses from traveling to the brain. They are applied on the skin and penetrate a few millimeters in the skin. They block pain from the needle puncture but may not take away the pain from the injection of the vaccine because the vaccine is injected in the subcutaneous or intramuscular tissue, which is deeper than only a few millimeters. Dr. Shah reviewed the 3 products available in Canada, including EMLA<sup>®</sup> (lidocaine-prilocaine), Ametop<sup>®</sup> (amethocaine or tetracaine) and Maxilene<sup>®</sup> (liposomal lidocaine). She stated that they required different application times: EMLA<sup>®</sup> (60 minutes), Ametop<sup>®</sup> (30-40 minutes), Maxilene<sup>®</sup> (20-30 minutes). There is a theoretical risk of methemoglobinemia with EMLA<sup>®</sup>, which is a condition characterized by the inability of red blood cells to carry oxygen, but it has only ever occurred in overdose situations and is reversible after administration of an antidote. Dr. Shah stated that all of the products were available without a prescription.

Altogether, 833 infants and children have participated in studies of EMLA<sup>®</sup> for different vaccines. The percent reduction in pain from the needle puncture ranges from 6-44%, depending on how pain is measured. For Ametop<sup>®</sup>, 238 infants and children have participated in trials. Pain has been reduced by 35-64%. To date, no studies have been performed with Maxilene. We would expect it to have similar effects as EMLA<sup>®</sup> and Ametop<sup>®</sup>.

For sweeteners, sucrose solutions (sugar water) have been most frequently studied. Dr. Shah stated that it is not clear how sugar water works, but that it might help the body release its own 'natural painkillers.' Sugar water is frequently used to treat pain in hospitalized newborn infants. Altogether, 633 infants ranging from 2-6 months have participated in studies of sucrose to manage immunization pain. Sucrose leads to a 13-73% reduction in pain. Another sugar, glucose, has been studied in 110 infants, with a 22-62% reduction in pain.

Coolants are chemicals and when sprayed on skin, reduce the skin temperature and cause temporary numbing. Altogether, 3 have been tested and a reduction of 8-32% in pain has been observed. Coolants may not be accepted by young infants and children, however, as the cold sensation may be perceived as painful. Dr. Shah was unaware of the commercially available products.

Oral analgesics (acetaminophen-Tylenol<sup>®</sup>, Tempra<sup>®</sup>; ibuprofen-Motrin<sup>®</sup>, Advil<sup>®</sup>) have not been demonstrated to reduce needle puncture pain. In recent studies, their use has not been shown to prevent side effects that occur after the needle (such as fever, swelling, pain) either. They should only be used if needed.

## **5. Effects of Topical Local Anaesthetics on Immune Response**

Dr. Michael Rieder, Clinical Pharmacologist and Paediatrician, University of Western Ontario, reviewed the evidence for whether topical local anaesthetics interfere with the immune response to the vaccine.

Dr. Rieder began his presentation with a brief overview of the importance of pain management and stated that dramatic improvements have been made in emergency departments over the last 15 years as a result of research on pain in childhood. He stated that there has been a culture shift to ‘painfree’ and ‘atraumatic’ care in emergency departments. Pain reduction strategies should be part of public policies on immunization.

Dr. Rieder stated that the purpose of immunization is to provide a specific, brisk and robust immune response with the capacity for expansion, to protect against disease. Pain reduction strategies cannot reduce this response; otherwise they would interfere with the goals of vaccination. In laboratory studies, local anaesthetics (lidocaine mostly, which is present in EMLA<sup>®</sup> and Maxilene<sup>®</sup>; followed by amethocaine, which is present in Ametop<sup>®</sup>; and then bupivacaine), do alter immune effects – they cause changes in leukocyte responses and cytokine profiles. However, studies performed in the laboratory are not necessarily transferable to living organisms. Moreover, the doses that have been used are extremely large, and maybe lethal if given to a living organism. To date, only 2 studies in post-surgical humans were identified, whereby local anaesthetics or systemic analgesics did not demonstrate an effect on immune response.

The effects of topical local anaesthetics (EMLA<sup>®</sup> or Ametop<sup>®</sup>) on immune responses during immunization have been evaluated in 3 studies involving a total of 382 infants. No changes in immune responses have been observed. Immune responses were measured by antibody titres. We don’t know about actual vaccine failure, because we would need a huge population of hundreds of thousands of people to show that. Antibody titre is used as a conventional measure of immunization success.

In summary, local anesthetics probably don’t affect immune response. It is unlikely that we will ever get a definitive answer; no one will fund such a study. We have to base public policy on the best available evidence, and on reasonable extrapolation. It would be reasonable to conclude pain control for immunization with topical local anaesthetics is safe.

## **6. Systematic Review of Psychological Interventions for Reducing Pain during Immunization**

Dr. Christine Chambers, Paediatric Psychologist and Pain Scientist, Dalhousie University, reviewed the evidence for psychological analgesic interventions. Dr. Chambers stated that psychological interventions that are used for medical procedures are cognitive-behavioural interventions. The cognitive component was defined as what is known, believed or felt; and the behavioural component was defined as what is learned by observation, reward, punishment, or other peoples' reactions. The technique used depends on the child's age.

Dr. Chambers described specific techniques: distraction (focusing attention on another activity); cognitive coping skills ("I can do this"); imagination and imagery; hypnosis (deep sense of relaxation where imagery and suggestion can be used); breathing exercises; relaxation; modeling; behavioural rehearsal; reinforcement; parent involvement. Dr. Chambers illustrated the application of some of the techniques with video clips.

She stated that in a systematic review involving 713 children undergoing immunization, psychological interventions reduced pain responses by 20-30%. The specific interventions used include: distraction, nurse coaching, coping skills, deep breathing, demonstration and parent participation.

Dr. Chambers demonstrated how these interventions could be used in clinical practice. She showed a video clip where skills were being taught to the viewer (children and parents) by a muppet, which can be used in the waiting room. Dr. Chambers also recommended developing kits/baskets for families, that included items such as bubbles, stress balls, ideas for things to do when in pain, and brochures for parent with age-appropriate pain management techniques.



## **7. Systematic Review of Injection Techniques for Reducing Pain during Immunization**

Dr. Moshe Ipp, Paediatrician and Associate Professor, SickKids and University of Toronto, reviewed the scientific evidence for injection techniques that may help in reducing pain during immunization. He began his presentation by stating that the worldwide burden of immunization is huge: the Center for Disease Control, USA, estimates that 12 billion injections are given annually and the World Health Organization estimates 100 million are given to children. He indicated that the most common question asked by children on a visit to their doctor is “Am I getting a needle today?” The impact of this pain workshop on identifying and helping implement factors that reduce the pain of vaccination is therefore massive.

Dr. Ipp stated that there is great variability in how vaccines are administered. His presentation reviewed the evidence for reducing pain in three major areas: injection method (speed of injection, aspiration, angle, needle length and gauge, injection of an air bubble, needle change, pressure applied to the injection area), administration site [body (arm or thigh), tissue (subcutaneous or intramuscular)], and vaccine factors (type/pharmaceutical formulation, order of injection, temperature, sequential/simultaneous injection).

In reviewing the recommendations for vaccine injection, Dr. Ipp noted that for decades the recommendations have been based on expert opinion alone, without adequate scientific evidence to validate its effectiveness or safety. These recommendations include: a rapid plunge of the needle into the skin, followed by aspiration for 5 –10 seconds to ensure that a blood vessel has not been penetrated (although the US Red Book on Infectious Diseases now recommends that aspiration is not necessary; while the Canadian Immunization Guide, is less emphatic and continues to state that aspiration may be performed). After aspirating the vaccine material should be injected slowly, and then the needle slowly withdrawn from the injection site. In a 2005 survey, Dr. Ipp showed that 71% of pediatricians and nurses continue to aspirate before vaccination, but they do so for less than 5 seconds, which essentially renders the procedure ineffective for the intended purpose of detecting a flush back of blood, so they might just as well not perform the procedure. If aspiration is done too quickly, it causes collapse of the small blood venule because of the small needle used, so that the flush back of blood will not be observed.

Dr. Ipp reviewed the evidence of how infant’s pain responses are affected following a slow vaccine injection technique with aspiration compared with a rapid injection with no aspiration. In a 2006 study of 113 infants, the rapid injection technique with no aspiration was demonstrated to reduce the percentage of infants that cried at the time of immunization from 82% to 42%. The average duration of crying was also significantly reduced from 37 seconds to 11 seconds in the rapid injection group.

Dr. Ipp reviewed the evidence for the effect of different needle lengths on pain responses during immunization. He indicated that there have been 4 studies done to date, in which local skin reactions were used as the primary outcome measure, a proxy for pain. In general, all demonstrated an advantage of longer needles over shorter needles, with an optimal overall needle length of 1 inch. The American Academy of Pediatrics states that needle length should be chosen

based on age, weight and size of the child: for newborns and infants, 5/8 inch needle; for toddlers to adolescents, 1 inch needle; for large adolescents, 1.5 inch needle.

There are 2 studies that have investigated the effect of needle gauge, but both had methodological limitations. The optimal needle gauge appears to be 23-25 gauges.

For intramuscular vaccination, regarding the effect of the angle of injection on pain responses, there have been 3 published guidelines: The US guideline recommends a 45 degree angle; the World Health Organization (WHO) recommends a 90 degree angle; and the Australian guideline recommends a 45-60 degree angle. In Canada, the 90 degree WHO guideline is followed, (injecting intramuscular injections at a 45-degree angle may lead to inadvertent subcutaneous injection rather than intramuscular injection causing more pain). In a study comparing the three techniques, the WHO 90 degree angle caused the least local reaction.

Dr. Ipp pointed out that for subcutaneous injections a 45 degree angle is recommended.

Dr. Ipp stated that there are no published studies in children undergoing immunization that have investigated the effect of applying pressure on the site before injection. However in studies where the site was massaged after the injection was administered, there was no benefit and there was an increase in pain and local reactions. Massaging the injection site after vaccination is therefore not recommended.

Dr. Ipp stated that there are no studies that have investigated the effect of speed of injection on immunization pain.

Dr. Ipp reviewed evidence for a difference in pain according to the body site of injection. It has been shown that in 18-month old infants, injections in the anterolateral thigh cause more pain (limping and reduced limb movement) than injections in the deltoid muscle of the arm. It is recommended that in infants under 1 year of age, the anterolateral thigh should be used, whereas in toddlers and children greater than 1 year, the deltoid muscle should be used.

Dr. Ipp reviewed evidence in favour of intramuscular injection over subcutaneous injection; intramuscular injection has been shown to cause about 20% less pain. He commented, however, that the tissue site in which vaccines are injected is determined by the vaccine type; live attenuated vaccines should be administered subcutaneously and killed vaccines intramuscularly.

Dr. Ipp then discussed aspects of the vaccine components and their potential effect on pain. He stated that pain from different vaccines might vary due to differences in the chemical composition of the product, including: pH (acidity), adjuvants (additives), antigen and osmolality. He reviewed 4 studies comparing 2 interchangeable vaccine products (Priorix<sup>®</sup> and MMR-II<sup>®</sup>). He stated that anecdotally, it was noted that MMR-II<sup>®</sup> was more painful than Priorix<sup>®</sup>. When evaluated formally in randomized controlled trials, 4 different studies substantiated that Priorix<sup>®</sup> was 40-100% less painful than MMR-II<sup>®</sup>.

More recently, Dr. Ipp has compared the pain from 2 completely different vaccines: Pneumococcal conjugate vaccine (Prenar<sup>®</sup>) and DPTaP-Hib (Pentavalent<sup>®</sup>). In that study, 3% of

the infants vaccinated with DPTaP-Hib did not cry compared to 32% of infants vaccinated with Prevnar. It was also shown that if the less painful DPTaP-Hib vaccine was administered first, there was less pain overall. Dr. Ipp commented that the pharmaceutical industry must include evaluations of pain in the vaccine drug development stage.

Dr. Ipp stated that there were no studies demonstrating a benefit from any of the following maneuvers: warming the vaccine prior to injection; simultaneously injecting multiple vaccines rather than sequentially (although simultaneous injection is preferred by parents); injecting air bubbles into the muscle to clear the bore of the needle; and changing the needle prior to injection (although comments were made by the audience that needles that are re-used may be duller than new needles).

Dr. Ipp concluded that the best way to minimize pain at the time of vaccination comprises the following steps: rapid intramuscular injection at 90 degrees and without aspiration; using longer, smaller gauge needles, use of anterolateral thigh for infant <1 year, and deltoid for child >1 year, and administration of the least painful vaccine first.

## **Summary of Open Discussion / Workshops**

### **1. Summary of Evidence**

- Pain during immunization is a significant burden for children and their families.
- Effective analgesic techniques exist and are not being used.
- Based on the systematic reviews, the following strategies are recommended for reducing pain during immunization:
  - Topical local anaesthetics
  - Vapocoolants
  - Sweetening agents - sugar water (young infants only)
  - Psychological cognitive-behavioural techniques
  - Priorix<sup>®</sup> instead of MMR-II<sup>®</sup>
  - Rapid injection without prior aspiration
  - Intramuscular injection at a 90 degree angle
  - Antero-lateral thigh for infants < 12 months old and deltoid muscle for those > 1 year
  - Administration of the least painful vaccine first.

## **2. Knowledge Gap/More Study Needed**

<b>Vaccine</b>
Use formulations with minimal pain during vaccine development stages and modify pharmaceutical products in order to reduce pain
Develop combined vaccines to minimize number of pokes
Test new vaccines with topical local anesthetics
Change vaccine schedule
<b>Topical Local Anaesthetics</b>
Risks of sensitization with repeated use (communicate to users)
Test new vaccines with topical local anaesthetics
Management of pain after injection (i.e., hours to days post-injection)
<b>Injection Techniques</b>
Pressure at site of injection
Change vaccine schedule
<b>Psychological Interventions/Physical environment</b>
Influence of environment on pain
<b>Overall Pain Experience</b>
Psychological and physiological effects of immunization
Amount and effective management of pain after injection (i.e., hours to days post-injection)

### **3. Barriers to Pain Management and Solutions**

<b>Barriers</b>	<b>Solutions</b>
Unavailability of vaccine products that are pain-free	Work with industry representatives to develop these or incorporate analgesics in clinical trials
Parents unaware of effective methods to manage pain	Parental education and outreach
Lack of awareness of methods to measure pain	Disseminate existing validated metrics
Perception that pain management will increase physician and/or staff time requirements	Time motion studies
Perception of financial barriers to topical anaesthetics	Education
Vaccine administration is performed by many different providers in many different settings	Education through guidelines, professional societies, provider training,
Provider habits are difficult to change	Education through guidelines, professional societies, physician training
Providers are not aware of the importance of managing pain	Education through guidelines, professional societies, physician training
Regulatory barriers with licensing of topical anaesthetics for use with some vaccines	Education through guidelines, professional societies, physician training; Perform studies to change labeling

#### 4. Target Groups for Knowledge Translation and Recommended Initiatives

List of Key Messages	List of Strategies
<b>Parents/Children</b>	
Vaccines are good Pain should be managed	Age appropriate book for kids Read to me literacy program DVDs for kids Focus on 0-18 months Parents magazines, new parent lists Partner with retailers Discharge hospital materials Websites (Baby Centre), Get physicians to endorse the message Provincial help line Parent to parent (play group) Posters RNs Family resource centre Public health Cultural sensitivities (translation of information)
<b>Nurses</b>	
Proper injection technique Pain management strategies Parent/patient education	Continuing medical education RNAO, family practice nurses association Pamphlet for parents Video for parents Guidelines and implementation tools Provincial guidelines for nurses Academic detailing (through ministry site visits) Public Health Agency of Canada (competency exams) Train the trainer
<b>Physicians</b>	
Pain matters Proper injection technique  Parent/patient education  Professional duty to manage pain	In training curriculum Postgraduate training and continuing medical education Governing bodies of societies and organizations Endorsements of Royal College of Pediatrics Create guidelines define standard of care Grand rounds, conference, journal club

	<p>Newsletters</p> <p>Websites</p> <p>Academic detailing, pharma industry</p> <p>Ministry vaccine messaging</p> <p>Leverage parents to educate physicians</p> <p>Engage opinion leaders and expert panels</p> <p>Public Health Agency of Canada (competency exams)</p>
<b>Pharmacists</b>	
<p>Increase product visibility</p> <p>Cross-sell products</p> <p>Parent/patient advocate</p> <p>Integrate message with physicians and parents</p>	<p>Journals</p> <p>National and provincial pharmacy associations</p> <p>Meetings</p> <p>Posters</p>
<b>Ministry/Provincial government</b>	
<p>Teach everyone about pain management</p>	<p>Pain recommendations with immunization schedules</p> <p>Flyers in vaccine bags to pharmacy</p> <p>Website information</p>



## 5. Next Steps

Activities	Key Personnel
Steering Committee formation for future projects (oversight; funding, endorsement, timelines, communications)	Anna Taddio
Funding Opportunities (product development, assessment of effects, knowledge to action)	Anna Taddio
Workshop proceedings, peer reviewed articles and spin off summary endorsements	Anna Taddio, Michael Rieder, Vibhuti Shah, Christine Chambers, Moshe Ipp, Scott Halperin, Donna Lockett, Patricia Mousmanis
National Practice Guidelines and endorsements by key professional organizations	Bob Bortolussi, Patricia Mousmanis
National Immunization Strategies and core competencies	Mary Appleton
Children's book	Michael Rieder, Christine Chambers
Parent's guide	Ron Gold, Christine Chambers, Michael Rieder
Fact sheet for parents and providers	Vinita Dubey, Mary Appleton, Donna Lockett
Professional education materials	Patricia Mousmanis
Training video dissemination	Mary Appleton

## Appendix 1: Planning Committee and Plenary Speakers

Faculty	Organization or Specialty
<b>Dr. Christine Chambers</b>	Associate Professor of Pediatrics and Psychology, Canada Research Chair in Pain and Child Health, Dalhousie University and IWK Health Centre
<b>Dr. Scott Halperin</b>	Professor of Pediatrics and Microbiology & Immunology, CIHR/Wyeth Chair in Clinical Vaccine Research, Head, Pediatric Infectious Diseases, Director, Canadian Center for Vaccinology, Halifax, Dalhousie University
<b>Dr. Moshe Ipp</b>	Associate Professor of Medicine, University of Toronto, Pediatrician and Clinician Teacher, The Hospital for Sick Children
<b>Dr. Donna Lockett</b>	Knowledge Broker, The Hospital for Sick Children, Psychotherapist, Trauma Expert, Clear Solutions, Research Associate, University of Ottawa
<b>Dr. Michael Rieder</b>	Professor of Paediatrics, Physiology, Pharmacology and Medicine, University of Western Ontario, Associate Director of the Child Health Research Institute, CIHR-GSK Chair in Paediatric Clinical Pharmacology
<b>Dr. Vibhuti Shah</b>	Associate Professor of Paediatrics, University of Toronto, Neonatologist and Epidemiologist, Mount Sinai Hospital
<b>Dr. Anna Taddio</b>	(Project Leader) Associate Professor of Pharmacy, University of Toronto, Adjunct Scientist, The Hospital for Sick Children, CIHR New Investigator

## Appendix 2: Workshop Participants

Participant Name	Organization or Specialty
Ms. Mary Appleton	Sr. Manager, Canadian Coalition for Immunization Awareness and Promotion
Ms. Teresa Barozzino	Parent Representative
Ms. Laura Bickle	Managing Editor, Today's Parent magazine
Dr. Bob Bortolussi	Infectious Diseases and Immunization Committee, Canadian Paediatric Society
Dr. Katherine Boydell	Sociologist and Knowledge Translation Scientist, The Hospital for Sick Children
Dr. Vinita Dubey	Associate Medical Officer of Health, Division of Communicable Diseases, Toronto Public Health
Mr. Peter Fields	Manager, Public Health Policy & Government Relations, Merck Frosst
Dr. Ronald Gold	Professor Emeritus of Pediatrics, Faculty of Medicine, Former Head of Division of Infectious Disease, The Hospital for Sick Children
Mr. Richard Hamer	Vice President, Regulator/Clinical Affairs & Quality Assurance, Ferndale Labs. (also representing RGR Pharma)
Ms. Bernadette Kint	Family Health Manager, Toronto Public Health
Ms. Jocelyn Marcelo	Nurse Consultant, Vaccine Preventable Disease Control/Immunization Unit, Public Health Division, Ontario Ministry of Health
Ms. Ameeta Mathur	Manager, Vaccine Preventive Disease Program, Toronto Public Health
Dr. Patricia Mousmanis	Healthy Child Development, Ontario College of Family Physicians
Ms. Lori Palozzi	Advance Practice Nurse, The Hospital for Sick Children
Ms. Elena Parvez	Graduate Student, Pain Research, University of Toronto
Mr. André Picard	Public Health Reporter, Globe and Mail newspaper
Ms. Coleen Pollari	Nurse and Advisory Board member, Immunization Education Initiative
Dr. Stacey Pollock	Parent Representative
Ms. Janet Probst	Family Practice Nurse, Women's College Hospital
Mr. Ryan Pulleyblank	Research Coordinator, Pain Research, University of Toronto
Ms. Anne Resnick	Director of Professional Practice Programs, Ontario College of Pharmacists
Mr. Noel Saraza	Manager, Public Health Ontario, GlaxoSmithKline
Ms. Perica Sever	Professional Communications Manager, GlaxoSmithKline
Dr. Michael Sgro	Paediatrician (community and academic paediatrics)
Dr. Linda Sheahan	Palliative Care, Fellow in Bioethics, University of Toronto
Ms. Gina Watts	Sr. Market Manager/Analyst – Hospital Initiatives, Astra Zeneca
Dr. Hiro Yamashiro	Ontario Medical Association, Chair of the Section on Paediatrics

## Appendix 3: Workshop Flyer and Agenda

**MEETING**

### Conquering Pain: The Hidden Cost of Immunization

**January 28, 2008**  
**8:30 a.m. - 3:30 p.m.**

Leslie Dan Faculty of Pharmacy  
University of Toronto  
144 College Street, Toronto  
Room 1210, 12th Floor Board Room



The meeting is being organized by Dr. Anna Taddio, Associate Professor, Leslie Dan Faculty of Pharmacy, Adjunct Scientist, The Hospital for Sick Children, and Canadian Institutes of Health Research (CIHR) New Investigator.  
For more information contact Dr. Anna Taddio: Tel 416-978-8822, Fax 416-978-1833, E-Mail [anna.taddio@utoronto.ca](mailto:anna.taddio@utoronto.ca).



AGENDA OBJECTIVES

## Conquering Pain: The Hidden Cost of Immunization

This meeting will bring together the stakeholders that are needed for successful knowledge translation of pain management strategies during childhood immunization, including researchers and knowledge users.

The specific objectives of this workshop are to build a collaborative network, review and understand current research evidence and barriers to knowledge translation, and to develop strategies that will increase dissemination and use of research knowledge in this area.

8:30 a.m. **Breakfast**

9:00 a.m. **Welcome and Introductions**

Facilitator *Dr. David Shute, Greenfield Health*

9:15 a.m. **Mini Reviews**

Update on Vaccine Programs in Canada

*Dr. Scott Halperin, Infectious Disease Specialist and Vaccinologist*

Pain: The Hidden Cost of Immunization

*Dr. Donna Lockett, Knowledge Translation Broker and Psychologist*

Current Analgesic Practices: Results of a Pain Audit

*Dr. Anna Taddio, Pharmacist and Pain Scientist*

10:00 a.m. **Break**

10:30 a.m. **Evidence-Based Analgesic Interventions**

Systematic Review of Analgesic Interventions: Topical Anaesthetics and Oral Analgesics

*Dr. Vibhuti Shah, Epidemiologist and Neonatologist*

*Dr. Michael J. Rieder, Paediatrician and Clinical Pharmacologist*

Systematic Review of Psychological Interventions

*Dr. Christine Chambers, Psychologist and Pain Scientist*

Systematic Review of Injection Techniques

*Dr. Moshe Ipp, Paediatrician and Clinician Teacher*

11:30 a.m. **Workshop 1: Review of Evidence** What knowledge can we apply today?

12:30-1 p.m. **Lunch**

1:00 p.m. **Workshop 2: Review of Strategies** What are the strategies we can use to translate this knowledge into practice?

2:15 p.m. **Workshop 3: Action Steps** What, Who and When?

3:15 p.m. **Wrap-Up**

3:30 p.m. **Meeting Adjournment**

The venue is the Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Toronto, Ontario, M5S 3M2.

An information package for travel and hotel arrangements will be mailed to out-of-town guests separately.

For more information contact Dr. Anna Taddio: Tel 416-978-8822, Fax 416-978-1833, E-Mail [anna.taddio@utoronto.ca](mailto:anna.taddio@utoronto.ca).

## Appendix 4: Workshop Participant Survey

	<b>Pre-workshop</b>	<b>Post-workshop</b>
<b>Knowledge</b>	1-Poor, 2-Fair, 3-Good, 4-Excellent	1-Poor, 2-Fair, 3-Good, 4-Excellent
Understanding of why pain reduction among children is relevant	3	3.8
Understanding of how to effectively reduce pain experience among children	2.5	3.7
Understanding how you/your organization can help	2.5	3.3
<b>Attitudes and Beliefs</b>	1-Strongly disagree, 2-Disagree, 3-Agree, 4-Strongly agree	1-Strongly disagree, 2-Disagree, 3-Agree, 4-Strongly agree
Preventing pain in children during medical procedures is important	3.7	4.0
Getting the word out about how to prevent pain is a priority	3.5	4.0
I should be doing more to ensure children undergoing painful procedures experience minimal pain	3.5	3.8
<b>Barriers to changing practice and policies regarding minimizing pain</b>	1-Not a barrier, 2-Minor barrier, 3-Significant barrier, 4-Major barrier, 5-Insurmountable barrier	
Competing priorities	2.8	
Lack of awareness among practitioners of the importance of reducing pain	3.3	
Lack of awareness among practitioners of how to reduce pain	3.4	
Lack of know-how concerning how to engage in policy makers	3.2	
Lack of access to funding/resources	3.1	
<b>Strategies to get the word out about minimizing pain</b>		
Journal publications	82%	
Conference presentations	74%	
Workshop presentations	59%	
Presentations to non-academics	63%	
Media	82%	
Policy briefings	30%	
Summary brochures/pamphlets	63%	
Summary of key messages	41%	

Values are average scores or percent; number of respondents/question was 23-27.

## Appendix 5: Workshop Evaluation

Workshop Evaluation	Results
Length just right	85%
Number of participants just right	100%
Mix of participants just right	85%
Design/format (from 1=really liked the design to 5=did not like design)	2.1
Number of non-faculty participants willing to help with next steps	11

Values are average scores, number, or percent; number of respondents/question was 26-27.

## Appendix 6: Glossary of Terms

**Adjuvant**, A substance (e.g. aluminum salt) that is added during production to increase the body's immune response to a vaccine.

**Analgesic drug**, A medicine that leads to an absence of pain in response to stimulation which would normally be painful. Analgesic drugs that reduce acute procedural pain such as vaccine administration pain include topical local anaesthetics and sweetening agents (e.g. sugar).

**Anterolateral thigh**, Outside part of the mid thigh

**Antibody**, A protein found in the blood that is produced in response to foreign substances, e.g. bacteria or viruses, invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.

**Antigen**, Any substance, usually a protein that is capable of inducing an immune response.

**Aspiration**, Pulling back on the syringe plunger to detect if there is a flush back of blood

**Deltoid**, Outside part of the mid upper arm

**Immune**, A state of being protected against infectious diseases by either specific or non-specific mechanisms (i.e. immunization, previous natural infection).

**Immunization**, The process by which a person becomes protected against a disease. This term is often used interchangeably with vaccination or inoculation.

**Pain**, An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience.

**Titre**, Refers to the levels of antigen-specific antibody produced following vaccination.

**Vaccine**, A suspension of weakened or killed microorganisms or fractions thereof (i.e. purified protein subunits, polysaccharides, or split virions) that are usually administered intramuscularly (within a muscle), or subcutaneously (below the skin), to induce immunity and prevent infectious disease. Vaccines that were highlighted in the workshop include: DPTaP-Hib, Diphtheria. Polio, Tetanus, acellular Pertussis, Hemophilus Influenzae b vaccine; MMR, Measles Mumps Rubella vaccine (MMR-II<sup>®</sup> and Priorix<sup>®</sup>); Pneumococcal conjugate vaccine.

**WHO**, World Health Organization.

Sources for glossary:

<http://www.cdc.gov/nip/webutil/terms/glossary.htm>

[http://www.iasp-pain.org/AM/Template.cfm?Section=Pain\\_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728](http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728)