

Report to SAGE on reducing pain and distress at the time of vaccination

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Executive Summary

Although pain that develops in the hours to days after an injectable vaccine is relatively well-studied, significantly fewer resources and recommendations have been developed to prevent or mitigate pain or distress at the time of vaccination. Injection pain has been shown to cause distress for children and adults and onlookers, including health personnel giving the injection.

Fear of an injection as a result of poorly managed procedure pain can lead to vaccine hesitancy. A delay or avoidance of future vaccinations is associated with lower vaccination coverage rates which puts the individual and the public's health at risk due to the potential for outbreaks of vaccine-preventable disease. To address this iatrogenic harm at the vaccination event in the vaccination process, the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) identified the prevention and mitigation of pain and distress at the time of vaccination as one strategy to address vaccine hesitancy.

An evidence based approach was used to adapt existing evidence reviews and to develop recommendations relevant for low and middle income country settings. Some of the strategies to mitigate pain and distress at the time of vaccination will be familiar to practitioners but the evidence base and the imperative to act to prevent pain and distress are new. The evidence for each of the recommendations pragmatically incorporated low and middle income countries (LMIC) patient values and preferences, estimates on impact on equity, and the feasibility, acceptability and costs of the intervention.

The recommendations were developed for consideration at the SAGE April 2015 meeting. They relate to interventions to reduce pain and distress at the time of vaccination, as well as on strategies for implementation. Interventions that were impractical (e.g. such as those requiring substantial resources to implement), ineffective, potentially harmful, and/or without evidence of effectiveness, were not recommended.

Research and implementation gaps relevant for global settings were identified.

The following examples serve to highlight a few of the evidence-based recommendations. For a more complete list of recommendations please see the report:

- Do NOT aspirate when giving vaccines to all ages (strong recommendation)
- Administer vaccines from the least to the most painful vaccine for all ages (strong recommendation)
- Breastfeed at time of vaccinations for infants (conditional recommendation: for women who are breastfeeding and for whom breastfeeding during the vaccination session is culturally acceptable in the vaccination setting)
- Use neutral words at the time of vaccination; avoid language that increases anxiety (strong recommendation) for all ages

Introduction

Background

The relief of pain or distress during health-related procedures is a basic human right.¹ In recent years, there has been an increasing emphasis on measuring and tracking adverse effects from vaccinations. Although pain that develops in the hours to days after an injectable vaccine is relatively well-studied, significantly fewer resources have been devoted to understanding and mitigating pain at the time of the vaccination event. The Child-Friendly-Healthcare Initiative, developed by Child Advocacy International in the UK and endorsed by WHO and UNICEF, has recommended the development of standards and guidelines for the assessment of pain and discomfort, and that invasive procedures must be accompanied by adequate analgesia.² Pain at the time of vaccine injection has been defined as an Adverse Event Following Immunization (AEFI) from global research collaborations such as the Brighton Collaboration, and in need of assessment and management from the global immunization community.^{3,4} Furthermore, at the October 2014 SAGE meeting, the Working Group on Vaccine Hesitancy identified the mitigation of pain at the time of vaccination as one strategy to address vaccine hesitancy.⁵ Vaccine injection pain and/or fear of needles are documented concerns for vaccine recipients, caregivers, and those giving the injection, and are documented to lead to hesitancy.⁶ However, no evidence on strategies for the mitigation of pain at the time of vaccination pain has been retrieved in the systematic reviews of strategies to address hesitancy.^{7,8} To date, WHO has not provided any specific guidance document about how to mitigate pain at the time of vaccination.

Burden of pain and distress during vaccination

Vaccine injections are a common source of iatrogenic pain in childhood.⁹ Fear of needles is extremely common. In a survey on the prevalence of needle fears in children, 63% of children and 24% of adults reported they were at least a little afraid of needles. Approximately 40% of parents are concerned with pain during childhood vaccinations, 85% believe that doctors and nurses have a responsibility to make vaccinations less painful, and 95% wish to learn how to reduce pain in their children.^{6,10} Furthermore, the most common concern for parents of children receiving multiple injections in one visit was pain.¹⁰ A recent study from South Africa examining attitudes toward the use of multiple injections found them to be acceptable by health care workers and by parents but called for strategies to mitigate pain.¹¹

Research from high income countries has shown that pain at the time of vaccination has effects on the individuals involved in the administration and receipt of vaccines, and society more broadly.³ The person receiving the vaccine is subjected to the possibility of pain, and the experience can be negative not only for the vaccine recipient but also for health care providers and other onlookers such as parents, guardians and siblings.³ Fear and worry about the pain may intensify the experience of pain.^{12 13 14 15} Longer term, repeated painful and negative experiences with vaccinations can lead to avoidance of future vaccination³ putting the individual and the public's health at risk. Furthermore, people distressed by receipt of vaccines may be more likely to avoid needle-procedures in other areas of health care, leading to poorer health outcomes.³ Interventions to mitigate pain and fear during vaccination and prevent the potential negative long-term consequences but have been underutilized.³

Measuring pain

There are four general ways to assess pain: self-report measures, behavioural measures, observer reports, and physiological measures. Because pain is subjective, self-report measures are generally assigned the most weight. Different self-report measures are recommended at different ages. For example, children 3-4 years old may use the *Pieces of Hurt Tool*, pointing to the number of circles corresponding to their level of pain. Children 4-12 years may use the *Faces Pain Scale-Revised* which has them select the facial drawing corresponding to the level of pain expression they are feeling.¹⁶ Children 8 years or more and adults can use the *Numerical Rating Scale*.¹⁷ Behavioural measures can be used to provide information about pain. Validated tools such as the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) assess a broad band of behaviours such as crying, facial expression, leg positioning, and others, for a total score between 4-13.¹⁸ Similar tools include the Face, Legs, Activity, Cry, Consolability Observational Tool (FLACC)¹⁹ and the Modified Behavioural Pain Scale (MBPS).²⁰ Behavioural measures also include tools that rely on fine-grained coding of facial expressions, such as the Neonatal Facial Coding System (NFCS), Child Facial Coding System (CFCS), and Facial Action Coding System (FACS).¹⁹ Observer reports typically involve having observers (e.g., parents, health professionals) use some of the same tools used by children to provide self-reports (e.g. faces scales).

Physiological measures examine changes in body processes such as heart rate, vagal tone, respiratory rate, oxygen saturation, palmar sweating, skin blood flow and intracranial pressure. Physiological measures are not specific to pain and have been shown to habituate to pain and are therefore not very valuable as an outcome measure of pain.

There is no simple relationship between the amount of tissue damage and pain. Anticipatory anxiety (or fear) can impact on the pain experience. As such, it is important to mitigate not only pain but fear as well. Since proxy reports and observational methods typically cannot distinguish between fear and pain, the term used to describe what is being measured by them is distress. While this report focuses on pain as the over-arching concept, the words fear and distress are also used throughout to describe the evidence base for included interventions, as relevant.

Evidence based clinical practice guidelines

In 2008, the *Help ELiminate Pain in KIDS Team (HELPinKIDS)* was assembled in Canada. This independent, multi-disciplinary team was tasked with addressing the gap between numerous evidence-based treatments to mitigate vaccination pain and the fact that many individuals do not benefit from their use.³ The HELPinKIDS team synthesized the research evidence and published the first Clinical Practice Guideline (CPG) on this topic in 2010.⁹ Due to numerous new studies as well as demand from stakeholders to address new interventions, the HELPinKIDS CPG was updated in 2015.³ The expanded and updated *HELPinKIDS&Adults 2.0 Clinical Practice Guideline for Reducing Pain and Fear from Vaccine Injections in Children and Adults* formed the basis for the recommended interventions.

Technical consultation group members

In order to determine if and how the Canadian clinical practice guidelines could be adapted to WHO recommendations, a technical consultation was held on 16-17 February 2015 at WHO HQ in Geneva. The group of experts invited for the consultation and contributing to this report was composed of:

1. K. O. Antwi-Agyei, Immediate Past National Programme Manager, Expanded Programme on Immunisation, Disease Control and Prevention Department, Ghana Health Service, Accra,

Ghana (expert consultant, also member of the WHO Immunization Practices Advisory Committee)

2. Christine Chambers, Professor, Departments of Pediatrics/Psychology and Neuroscience, , Dalhousie University, and Centre for Pediatric Pain Research, IWK Health Centre, Halifax, Nova Scotia, Canada (co-author of HELPinKIDS&Adults 2.0 CPG)
3. Liesbet Goubert, Professor, Department of Experimental-Clinical and Health Psychology, Ghent University, Belgium (expert consultant)
4. Darunee Jongudomkarn, Associate Professor, Faculty of Nursing, Khon Kaen University, Thailand (expert consultant)
5. Noni MacDonald, Professor, Department of Paediatrics, Dalhousie University, IWK Health Centre and Canadian Center for Vaccinology, Halifax, Nova Scotia, Canada (co-author of HELPinKIDS&Adults 2.0 CPG)
6. Anna Taddio, Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, and Senior Associate Scientist, The Hospital for Sick Children, Toronto, Ontario, Canada (Lead author of HELPinKIDS&Adults 2.0 CPG)
7. Nikki Turner, Associate Professor and Director, Immunisation Advisory Centre, University of Auckland, New Zealand (SAGE Focal Point) – Participated in the consultation via phone connection

Lidia Oliveira, Senior Medical Manager - Europe – Vaccines, Pfizer also contributed on the phone to the discussions on the industry perspective for which she served as an industry representative.

The technical consultation and/or report writing was supported by the WHO's SAGE Secretariat (Philippe Duclos, Neeta Gurnani, Kevin Pottie, Melanie Schuster, Winnie Siu). Philippe Duclos, Neeta Gurnani, and Winnie Siu attended the face-to-face technical consultation.

It was agreed that the focus of the consultation would be on mitigation of pain, distress and fear during the vaccination event; i.e., acute pain (not delayed pain, which occurs in the hours to days thereafter) and that specific interventions for individuals with high levels of needle fear would not be included, but with the understanding that reducing pain will likely also prevent the development of high levels of needle fear in the future.

The group would like to acknowledge the work of Meghan McMurtry, Assistant Professor, Guelph University) who allowed the timely updating of the analysis of HELPinKIDS&Adults 2.0 CPG from which this report benefited.

Declaration of Interests

All invited experts except Lidia Oliveira, the industry representative, completed a declaration of interests. Two experts reported relevant interests. All interests were assessed not to constitute a conflict of interest in regard to contributing to the technical consultation. It was concluded that all members could take part in full in all of the discussions. The industry representative did not participate in discussions other than that of the industry perspective and was not involved in decision-making. The complete Declaration of Interests can be found in Appendix 1.

Methods

Overview

We used the *GRADE_DECIDE* process to adapt existing evidence for low and middle income country (LMIC) and differing geographical and cultural settings. This method included identifying potential interventions relevant and culturally acceptable for LMIC, identifying systematic review evidence to determine the trade-offs between benefits and harms, and then using literature and expert advice to explicitly document estimates for patient values and preferences, equity impacts, feasibility, acceptability, and costs. This process provided the evidence to determine interventions which were recommended and interventions which were not recommended.

Systematic review evidence

The 2015 HELPinKIDS&Adults 2.0 Clinical Practice Guidelines project selected and reviewed 55 different interventions designed to mitigate pain and fear during immunization injections.ⁱ In total, 136 articles were reviewed which had a predominance from high-income countries and the region of the Americas but included representation from every WHO region (see Figure 1).

WHO Regions- 136 Articles Reviewed for HelpinKIDS 2.0 Guideline

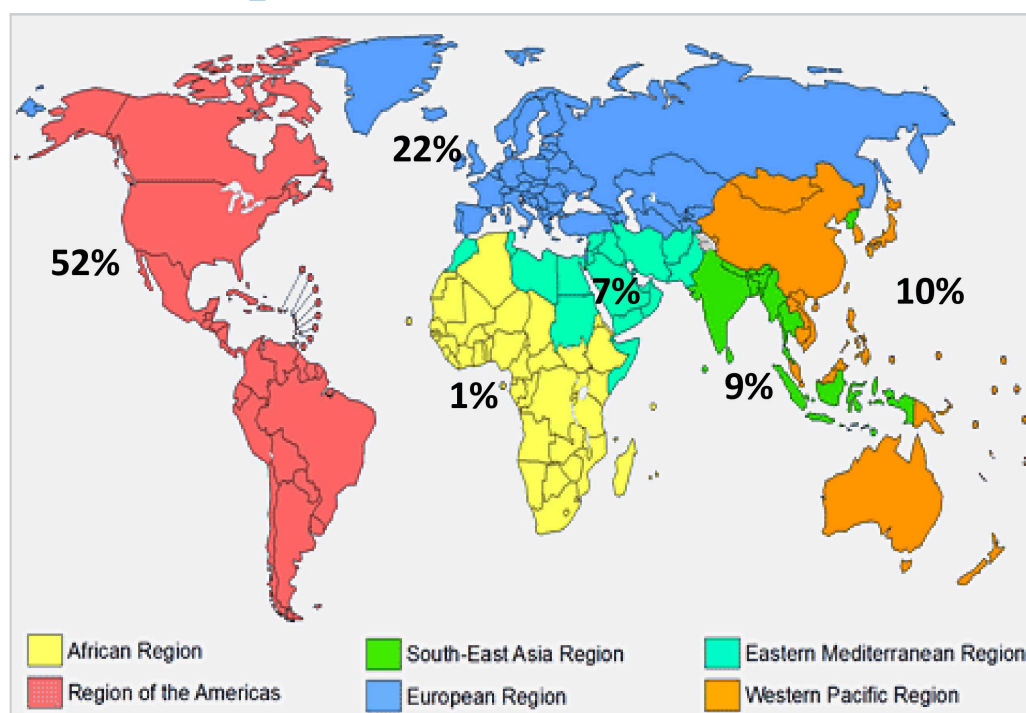


Figure 1: Percentage of reviewed articles by WHO region

The evidence-based GRADE (Grading of Assessments, Recommendations, Development and Evaluation)²¹ and Cochrane methodologies provided the general framework for the systematic

ⁱ As a result of the interaction in the context of the SAGE review, HELPinKIDS&Adults 2.0 was adjusted and the number of interventions reflected in this report departs from the initial set of 52 interventions listed in the project when the technical consultation took place. This report is consistent with the revised version of HELPinKIDS&Adults 2.0 accessible on the SAGE website.

reviews that were used to appraise and synthesize the research evidence and formulate the recommendations. The literature review considered randomized controlled trials and quasi-randomized controlled trials. As per GRADE methodology, interventions were rated on the strength of recommendation and the quality of evidence. In the HELPinKIDS&Adults 2.0 guidelines, the authors took a rigorous approach in grading quality of evidence and this often resulted in reporting high levels of uncertainty in the evidence.

Technical consultation at WHO

A technical consultation was held on 16-17 February 2015 at WHO HQ in Geneva in order to determine if, how and which of the HELPinKIDS&Adults 2.0 recommendations could be adapted to WHO recommendations. Importantly, the technical consultancy group was tasked with not only adapting recommendations from a high-income setting to lower income settings, but were also adapting clinical practice guidelines to guidelines for public health programs and policy. Three authors of the HELPinKIDS&Adults 2.0 CPG attended. As well, an expert in immunization and/or pain was invited from each WHO region; disciplines covered included psychology, nursing, pharmacy, medicine, pain research, vaccinology and immunization program management.

Choice of interventions

Prior to the technical consultation, participants of the technical consultation were provided with the entire review of evidence and guidelines from HELPinKIDS&Adults 2.0 CPG. To facilitate the proceedings of the technical consultation three members of the SAGE Secretariat independently ranked the most globally relevant recommendations out of 55 separate interventions addressed by HELPinKIDS&Adults 2.0 and relating to physical, psychological, pharmacological, procedural, or process interventions (these include 44 for the treatment of pain and of individuals undergoing vaccine injections, five process interventions and an additional six interventions for the treatment of fear in people with high levels of needle fears- the latter were considered out of scope for the development for the global guidelines). Then by consensus, the SAGE Secretariat and the three authors of the CPG prioritized interventions considered to be most globally relevant including for LMIC based on feasibility and cultural acceptability for discussion and adaptation during the technical consultation (in some cases by collapsing multiple recommendations into one more general intervention).

These prioritized interventions were:

1. no aspiration,
2. injecting the most painful vaccine last,
3. positioning (holding infant/child, sitting up, parental presence),
4. breastfeeding before and during vaccine injection,
5. topical anaesthetics,
6. sweet tasting solutions for infants,
7. distraction,
8. education of clinicians regarding vaccine injection pain and fear management, and
9. education of caregivers and individuals regarding injection pain and fear management.

The latter two interventions were later considered as part of the implementation process of other interventions rather than self-standing interventions and are reflected accordingly in this document.

An example of an intervention not prioritized for discussion included simultaneous injections as this was considered as impractical as it requires two health care providers working at same time.

During the technical consultation, detailed evidence for each of the prioritized interventions was presented and the considerations leading to them being recommended in the Canadian guidance document. The group then discussed the appropriateness of adapting each intervention to a global context considering cultural appropriateness, impacts on equity, availability, feasibility, acceptability, cost, and consistency with other WHO policies and recommendations (i.e., breastfeeding, nutrition, pain management, and injection practices).

Time was allotted during the technical consultation to systematically consider:

1. interventions that should explicitly be or not be recommended,
2. interventions where evidence was not clear enough to recommend them globally,
3. other interventions identified in the HELPinKIDS&Adults 2.0 project and not prioritized for discussion, and
4. other possible interventions not examined in the HELPinKIDS&Adults 2.0 but could be of use to mitigate pain during the vaccination event.

As a result additional interventions were added to the discussion (e.g., oral analgesics - see below).

Adaptation of the Canadian guidelines to WHO recommendations

In order to facilitate the adaptation of the Canadian clinical practice guidelines to WHO recommendations, group members were advised to consider the following questions, which were adapted from the evidence to decision *GRADE_DECIDE* guideline adaptation process (PLOS Medicine, in press):

Benefits and harms

- Are the identified benefits and harms relevant in the global context?
- Are there any additional benefits and harms that have not been considered?
- Are the benefits large compared to the harms?

Resource use and value for money

- What resources are required to implement this intervention (including human and monetary)?
- Are the costs worth the benefits?
- Are there any opportunity costs (i.e. by choosing this intervention, what opportunities are we giving up)?

Impacts on equity

- Would the intervention increase, decrease, or have no effect on health inequities?

Acceptability

- Is the intervention acceptable for patients, parents and health care workers?
- Are there any anticipated cultural barriers to this intervention?"

Feasibility (implementability)

- Is the intervention feasible to implement?
- If any special materials are required for this intervention, how feasible is it to procure them?

Other

- Are there any other issues to consider (e.g. any other relevant WHO policy recommendations)?

Formulating recommendations on interventions

The technical consultation group agreed by consensus that there was no need to update the relevant and recently conducted systematic review from the HELPinKIDS&Adults 2.0 project as it was both exhaustive and recent (last date for update of literature: Feb 26 2015). The group adapted and recommended a number of interventions for inclusion in health policy and public health programs to reduce pain, distress and fear during vaccination. The interventions were categorized by WHO age group as *“all ages,” “infants,” “children,” “adolescents,” or “adults (including pregnant and breastfeeding women).”*ⁱⁱ Some interventions were subcategorized under “conditional recommendations” in order to distinguish them as interventions which were recommended but may or may not be feasible or practical depending on context.

A list of interventions explicitly not recommended by the group was also determined, and again categorized by age. These interventions were further subcategorized as *“effective but not practical,” “unknown effectiveness,” “ineffective,” or “ineffective with potential harms.”* Practicality of an intervention encompassed multiple issues, including resource use, feasibility and acceptability.

Implementation and research questions

The technical consultation group formulated a number of recommendations for WHO and countries to ensure the successful implementation of the interventions. Furthermore, a number of research questions that would be helpful in informing future recommendations were identified and those most important from a global perspective prioritized.

Examination of the evidence

As described above, based on the preliminary evaluation of benefits and harms, cultural acceptability and feasibility, a subset of the interventions included in 55 clinical questions in the HELPinKIDS&Adults guideline prioritized in-depth review at the technical consultation group meeting. The focus of the discussion was global feasibility and acceptability, in particular for Low and Middle Income Countries. In some cases multiple interventions were collapsed in one more general recommendation.

The evidence on the benefits and harms for each of the interventions is taken directly from the 2015 HELPinKIDS&Adults Guideline (noted in quotation marks and italics) and as a result is categorized according to Canadian age groupings for which the relevant cut-offs may depart from that of WHO e.g. for adolescents as well as according to availability of the evidence. The specific

ⁱⁱ Infants 0-11 months, children 1-9 years, adolescents 10-19 years

2015 HELPinKIDS & Adults Guideline recommendation to which the passage refers is noted at the end of the quote. The source of the evidence is mentioned in each section but the specific references are not added in the list of references at the end of this document. For the complete list of references, please refer to the HELPinKIDS&Adults guideline posted on the SAGE website.

1. No aspiration

Aspiration i.e. pulling the syringe plunger before intramuscular injection to see if blood is aspirated is a long-standing practice in certain geographical areas that was initially proposed for safety reasons, i.e. to prevent injection in blood vessels.

Evidence: *“Aspiration may add to pain because of longer contact time and lateral movement (wiggling) of the needle. Three studies including individuals from infancy to adulthood were included in the systematic review (Girish et al., 2014, Ipp et al., 2007; Petousis-Harris et al., 2013). There was very low quality evidence for pain and distress (critically important outcomes) due to risk of bias and imprecision. In the single study that included 114 individuals able to provide self-report (Petousis-Harris et al., 2013, no evidence of a difference in pain between aspiration and no aspiration groups was demonstrated. In the two studies including 313 infants, there was a benefit of not aspirating on infant acute distress (Girish et al., 2014, Ipp et al., 2007): SMD -0.82 (95% CI -1.18, -0.46). The latter studies, however, were confounded by the speed of injection (i.e., slow injection speed for the aspiration group compared to a fast injection speed for the no aspiration group).”*

(HELPinKIDS&Adults 2.0 CPG Recommendation 1).³ The lack of benefit of not aspirating in the Petousis-Harris (2013) study may be due to: 1) a ceiling effect (peak pain experienced in both groups as soon as the vaccine was injected due to the high degree of pain from the vaccine used itself), 2) a floor effect (minimal difference in pain among techniques because of the small differences in duration of administration time between them), 3) age/participant-related effects (unclear what participants knew about the study and how this impacted their ratings of pain), or 4) a confounder (the authors describe that some vaccines were injected in a different anatomical site than intended and were potentially more painful. This probably occurred in the quick injection group and not the other groups).

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Benefits of no aspiration include shorter contact time with the needle and reduced potential for lateral movement (wiggling) of the needle, leading to less pain. There are no established harms.

Resource use and value for money: No additional resources are required for implementation other than education of providers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of not aspirating.

Feasibility (implementability): The intervention was seen as highly feasible.

Other: If the anatomical site for injection is chosen correctly, aspiration is not necessary; this is because recommended injection sites are not near major vessels. It is important to note that slight

bleeding after withdrawal of the needle does not indicate penetration of blood vessels, as minor surface vessels can be perforated during injection. The WHO recommends the exclusive use of auto-disable (AD) syringes for vaccinations so that they cannot be reused and most of these syringes do not allow for aspiration. Most LMIC follow this recommendation whereas most HIC do not. From this vantage point, LMIC are better equipped to reduce pain from vaccination because their syringes do not allow for aspiration.

2. Administer vaccines in order of increasing painfulness

Evidence: *“During many visits for routine childhood immunization visits, more than one vaccine injection is administered. It is known that some vaccines cause more pain during injection than others. Two studies including infants from 0 to 6 months were included in the systematic review (Ipp et al., 2009; Ravikiran et al., 2011). There was moderate quality evidence for distress, the critical outcome due to imprecision, and evidence of a substantial benefit when the most painful vaccine was injected last. Included studies compared either: 1) pneumococcus conjugate vaccine, PCV (Prenar™) to diphtheria and tetanus toxoids, polio, acellular pertussis, and Haemophilus influenzae type b conjugate vaccine, DPTaP-Hib (Pentacel™), or 2) BCG vaccine (TUBERVAC™) to hepatitis B vaccine (GeneVac-B™). PCV and hepatitis B caused lower overall infant acute distress (n=196) when given last: SMD -0.69 (95% CI -0.98, -0.40). No studies were identified that included individuals able to self-report pain.).” (HELPinKIDS&Adults 2.0 CPG Recommendation 2).*³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There are clear, positive benefits and no anticipated harms.

Resource use and value for money: No additional resources are required for implementation other than education of providers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of administering vaccines in order of increasing painfulness.

Feasibility (implementability): A significant limitation to implementing this intervention is that we do not yet have a way to rate the painfulness of different vaccines at the time of injection as this is not required information for licensure, and therefore are currently unable to advise vaccine administrators on the order in which vaccines should be administered. Health care workers may “know” which is the most painful vaccine through experience but no standardized comparative evaluations of pain at the vaccination event across different vaccines and different preparations is available. For vaccines for which painfulness is very similar and cannot be distinguished from experience, the order of sequencing likely is of no consequence. Based on feed-back from the field, global guidance on how to sequence vaccines or categories of vaccines could hopefully be provided in the near future for prequalified vaccines.

Other: Administering vaccines in order of increasing painfulness may prevent pain sensitization.

3. Positioning

Evidence: *“The intervention of positioning includes holding children ≤ 3 years of age as well as having all those over 3 years and adults sit up when receiving vaccinations. Individuals may be positioned in a number of different ways (e.g. sitting up, supine, etc.). Some positions are more comfortable and promote a greater sense of control.”*

Holding for those up to 3 years of age

Evidence: *“Three studies including 213 infants aged 6 weeks to 6 months were included in the systematic review (Hallstrom 1968; Ipp, Taddio et al., 2004; Taavoni et al., 2010). The intervention consisted of holding of the infant by a parent. Holding was initiated before vaccine injection(s) and continued during and after injection(s). There was low to very low quality of evidence across the different indicators of infant distress (critical outcome) due primarily to risk of bias from lack of blinding and imprecision, and there was no evidence of a benefit of holding. In the only analysis that included all studies (n=213), there was no evidence of a benefit on acute infant distress. However, there was contamination of the control (lying supine) group (i.e., some infants in the supine group were picked up and held immediately afterwards) in one of the studies (Ipp, Taddio et al., 2004). Removal of the data from this study led to a benefit in acute distress: SMD -1.25 (-2.05, -0.46). The results were not significant for the other distress outcome (i.e., acute and recovery phase); however, the data were obtained from the same flawed study (i.e., Ipp, Taddio et al., 2004).”* (HELPinKIDS&Adults 2.0 CPG Recommendation 9).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Evidence shows that holding a child aged up to 3 years helps alleviate some distress, and the child may be held by any caregiver, not just the parent. There are no anticipated harms.

Resource use and value for money: At minimum a chair is recommended for the person holding the child to increase comfort and promote safety (minimize risk of falls).

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of positioning. In some African countries, parents and children are very used to being watched while being immunized and positioning the child is not a problem from this perspective.

Feasibility (implementability): This intervention was seen as highly feasible. However, health workers will need to be trained on the implementation of this intervention on best positioning as well as how to best advise parents in a courteous manner as this latter aspect will also be important. Health care workers may need to adjust their own positioning in order to deliver vaccinations in a comfortable and safe manner.

Other: None

Sitting up during vaccine injections should be used in children over 3 years and in youth and adults

Evidence: *“One study including children aged 4 to 6 years was included in the systematic review (Lacey et al., 2008). There was low quality evidence for critical outcomes (fear, pain) due to risk of bias and imprecision. The results were mixed: a benefit was observed for fear [n=107; SMD -0.39, 95%*

CI -0.77, -0.01]] but not for pain (SMD: 0.07, 95% CI -0.31, 0.45). We considered the results for distress given that the children were of an age where self-report may not be reliable (Chambers 2002, von Baeyer, Forsyth et al., 2009). Both measured distress outcomes demonstrated a benefit of the intervention. There were no identified undesirable consequences.” (HELPinKIDS&Adults 2.0 CPG Recommendation 11).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Evidence shows that sitting up for those over 3 years and youth/adults may help alleviate fear and distress. For younger children this can be done sitting on a parent’s lap in a hug with child’s legs on either side of the parent’s lap and parent’s arms over the child’s arms to help the child to stay still. Older children, youth and adults sit on their own. Lying down may be preferred in those with a history of fainting; providing support or reclining may avoid falls from a seated position. There are no anticipated harms.

Resource use and value for money: At minimum a chair is required for the person receiving the vaccination or holding the young child. Alternatively, one could sit on the ground.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of positioning. In some African countries, parents, children and adults are very used to being watched while being immunized so positioning is not seen as a problem from this perspective.

Feasibility (implementability): This intervention was seen as highly feasible. However, health workers will need to be trained on the implementation of this intervention as the courtesy with which health care workers advise parents, children and adults on positioning will likely be very important. Health care workers may need to adjust their own positioning in order to deliver vaccinations in a comfortable and safe manner.

Other: None

4. Use of language to reduce pain and fear: neutral verbal cues for impending vaccination, repeated reassurance, and false suggestions of minimal pain

Evidence: *“When communicating with individuals during painful procedures, the use of language that is unnecessarily highly negative in valence has been discouraged. Similarly, providing false suggestions about the amount of pain involved (i.e., minimizing pain or lying about pain) and excessive use of reassurance are not generally recommended. Together, the use of these interventions have not been shown to reduce pain and may even increase pain. In the case of false suggestions, there is the potential to promote distrust.”* (HELPinKIDS&Adults 2.0 CPG).³

False suggestions of minimal pain

Evidence: *“Two studies including 240 children aged 4 to 6 were included in the systematic review (Eland, 1981; Fowler-Kerry & Lander, 1987). In both studies, children were given a placebo intervention (i.e., wearing headphones or air sprayed on the skin at the injection site) and told by the experimenter or clinician that something was being done to help them during the injection or to make the injection hurt less. Both studies examined the impact of adding suggestion to another*

intervention (i.e., distraction or vapocoolants) as well. There was low quality evidence for the critical outcome (pain) due to risk of bias (inconsistent or lacking of blinding and selective outcome reporting) and imprecision and no evidence of a benefit on pain. Since the inclusion of pain-relieving interventions with suggestions confounds the issue, the analysis was repeated excluding the data for pain-relieving interventions. The results were not altered. There was no evidence for the critical outcome of fear.” ((HELPinKIDS&Adults 2.0 CPG Recommendation 30).³ As previously stated, “The use of false suggestions of minimal pain (e.g., “it’s just a poke”) and lies (e.g., “it won’t hurt”) may promote distrust between any individual delivering such messages and individuals undergoing vaccination (Taddio, Illersich et al., 2014).”

Repeated reassurance

Evidence: “Two studies (Gonzalez et al., 1993; Manimala et al., 2000) including 82 children aged 3 to 7 years were included in the systematic review. In both studies, repeated reassurance by the parents was examined. Methods of training the parents in the use of reassurance varied between studies and included instructions, audio and live modeling, and practice; parents were also reminded throughout the procedure to use reassurance. There was very low to low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was no evidence of a benefit of reassurance in critical outcomes. There was very low quality of evidence for distress (important outcome) and no evidence of a benefit.” (HELPinKIDS&Adults 2.0 CPG Recommendation 31).³

Verbal signal about pain

Evidence: “Three studies including 391 adults undergoing venipuncture (Ott et al., 2012; Vijayan et al., 2015) or IV cannulation (Dutt-Gupta et al., 2007) were included in the systematic review. In all studies, individuals were given a verbal signal about the start of the procedure or a signal about the pain. One study specifically excluded individuals with significant needle fears (Ott et al., 2012). Data were available for the critical outcome of pain but not fear. For the critical outcome of pain, there was very low quality evidence due to risk of bias, indirectness, and imprecision, and no evidence of a benefit of the intervention.” Despite the lack of observed benefit, it is recommended that more neutral warnings or prompts about the procedure (e.g., “Here I go”) be used.” (HELPinKIDS&Adults 2.0 CPG Recommendation 29).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: Discussion with individuals undergoing vaccination and signalling the impending procedure is a routine part of the vaccination process to try to minimize sudden movements and elicit coping strategies in individuals. Evidence suggests that the use of language that enhances anxiety or is falsely reassuring or dishonest is not beneficial and may harm by increasing distress and decreasing trust. Separately, it has been demonstrated that threatening words undermine pain-relieving interventions.^{22,28} Neutral language is preferred. There is strong rationale across childhood for avoiding repeated reassurance. This recommendation applies to children of all ages as even if they are too young to understand the words, they may understand the tone of voice (which is hypothesized to be important to the effect of this intervention). Indeed repeated reassurance has been demonstrated in observational studies to be associated with higher distress in babies. There are less data for adults, but there is rationale to avoid excessive reassurance as repeatedly saying statements like ‘don’t worry it will be over soon’ are expected to be at least not helpful and potentially anxiety-provoking in older age groups. False suggestions about pain are to be avoided across the lifespan as they promote distrust. Note that even if the person getting immunized is a baby, parents will hear these messages and may become untrusting.

Resource use and value for money: The only additional resources required are that required to build messages on the use of language into existing education and training programs for healthcare workers.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding cultural acceptability.

Feasibility (implementability): This intervention was seen as feasible. However, health workers will need to be trained on the implementation of this intervention as use of neutral words and avoidance of anxiety provoking language is not necessarily widely done routinely.

Other: None

5. Caregiver presence

Evidence: Children are vaccinated in different settings and parents may or may not always be present. *“Four studies including 245 children aged 13 months to 9 years were included in the systematic review (Broome & Endsley, 1989; Gonzalez et al., 1989; O’Laughlin & Ridley-Johnson, 1995; Shaw & Routh, 1982). Parents were present (were not provided with any training with how to behave) or absent during their children’s vaccinations. There was very low quality evidence for important outcomes (distress in individuals unable to provide self-report, child preferences) and no data for critical outcomes (pain, fear). Extensive selective reporting bias, lack of blinding and a small sample size contributed to the quality rating. Results were mixed for different indicators of distress. Available evidence showed a strong preference by children to have their parents present (Gonzalez et al., 1989).”* (HELPinKIDS&Adults 2.0 CPG Recommendation 46).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: In general there is a dearth of literature around examining the benefits of having a caregiver present for vaccination. This is likely because in many high income countries such as Canada the assumption is that parents should/will be present, and research has instead focused on what parents are doing when present during vaccinations. Child preference should be attended to (e.g., occasionally fear on the part of a caregiver may accentuate fear for the child who thus may wish the caregiver not to be present).

Resource use and value for money: No additional resources are required for implementation as all infants and young children are accompanied by a caregiver for vaccinations.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding the cultural acceptability of having a caregiver present. In Thailand, guardian presence is a must but it does not have to be a parent; often an extended relative accompanies the infant or young child.

Feasibility (implementability): This intervention is highly feasible for infants. In some countries such as Belgium, school-based vaccination starts around 6 years of age so parents are not present. Therefore, this recommendation has been limited to the pre-school age.

Other: None

6. Breastfeeding

Evidence: *“Breastfeeding is one of the most significant factors in promoting optimal health and development in children and is the normative standard for infant feeding and nutrition (Gregory et al., 2014). Within the context of vaccination, there is evidence that breastfeeding may improve the effectiveness of some vaccines and reduce fever associated with vaccine injections (Dórea 2012; Pisacane et al., 2010).*

For the 2015 HelpinKids&Adults Guideline, breastfeeding was specifically evaluated for its effectiveness in reducing distress in young children during 2 different time points relative to vaccine injections: 1) during needle puncture and administration of the vaccine and 2) beforehand (i.e., before needle puncture and administration of the vaccine. When used during vaccine injections, breastfeeding is hypothesized to reduce distress via multiple mechanisms, including: physical comfort, sucking, distraction and ingestion of sweet-tasting and other substances that may have individually and together, have pain and distress-relieving effects. When used before vaccine injections, breastfeeding may reduce distress via satiation of infants, which may promote calmness during needle procedures.

Previous systematic reviews have demonstrated the effectiveness of breastfeeding undertaken during needle procedures in neonates and infants (Shah et al., 2009, Shah et al., 2012) and breastfeeding is used in hospital settings to reduce needle-related pain (Foster et al., 2013).” (HELPinKIDS&Adults 2.0 CPG).³

Breastfeeding at time of vaccination

Evidence: *“Nine citations that included data from 8 separate studies that examined breastfeeding **during** vaccination were included in the systematic review (Dilli et al., 2009; Efe & Özer, 2007; Goswami et al., 2013; Iqbal et al. 2014; Modarres et al., 2013; Abdel Razek & El-Dein, 2009; ShahAli et al., 2009; Taavoni et al., 2009 (same study as ShahAli et al., 2009); Thomas et al., 2011). Seven trials including 792 infants reported data for acute distress (Dilli et al., 2009; Goswami et al., 2013; Iqbal et al. 2014; Modarres et al., 2013; Abdel Razek & El-Dein, 2009; Shah Ali et al., 2009; Taavoni et al., 2009; Thomas et al., 2011). The quality of evidence for this outcome was low, downgraded for risk of bias due to lack of blinding and lack of consistent randomization across included studies. The SMD was -1.78 (95% CI -2.35, -1.22). The other distress outcomes included between one and four studies and all demonstrated a benefit of breastfeeding. The nature of the intervention prevents blinding and the sample size was small for some of the distress outcomes. The magnitude of benefit is substantial and valued highly”. (HELPinKIDS&Adults 2.0 CPG Recommendation 6).³*

Breastfeeding before vaccination

Evidence: *“Two trials including 100 infants aged 6 weeks to 3 months investigated the effect of breastfeeding **before** vaccine injections (Achema et al., 2011; Sahebihagh et al., 2011). The timing when breastfeeding ended was 2 minutes to 1 hour before vaccination. There was moderate to low quality evidence across all distress outcomes (critical outcome) due to risk of bias and imprecision. In the only analysis that included data from both studies, acute distress was lower in the infants in the*

breastfeeding group: SMD -1.43 (-2.14, -0.72). The results were mixed for other distress outcomes.” (HELPinKIDS&Adults 2.0 CPG Recommendation 7).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There are significant benefits to breastfeeding as WHO recommends exclusive breastfeeding for the first six months of life and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond.^{23,24} Therefore, there is a synergistic potential for this recommendation to align with those of infant nutrition. There are no known harms to breastfeeding. HIV infected mothers should be counselled to exclusively breastfeed in the first six months of life and continue breastfeeding thereafter unless environmental and social circumstances are safe for, and supportive of, replacement feeding. In circumstances where antiretrovirals (ARVs) are unlikely to be available, such as acute emergencies, breastfeeding of HIV-exposed infants is also recommended to increase survival.²⁵

Resource use and value for money: No additional resources are required for breastfeeding. Allowing time for a mother to breastfeed may be a constraint. Health care workers will need to be trained on being courteous and supportive of this intervention.

Acceptability: Breastfeeding in public is culturally acceptable in some places, such as Ghana, but not in others, such as Thailand. Furthermore, women may not want to breastfeed in front of male health care workers. For these reasons, this intervention can only be conditionally recommended.

Feasibility (implementability): WHO recommends exclusive breastfeeding until 6 months of age and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond, however many women do not breastfeed that long. It should be noted that sucking does not always occur spontaneously at the moment needed.

Other: Bottle-feeding (with pumped breast milk or use of formula) should have a similar effect as it closely mimics breastfeeding (holding, sweet tasting solution, sucking) but water supplies are not safe in all parts of the world. As stated above, WHO recommends exclusive breastfeeding for the first six months of life and that thereafter infants should receive complementary foods with continued breastfeeding up to 2 years of age or beyond. Therefore, bottle-feeding is not recommended universally as an intervention. However, if the child is already bottle-feeding at home then this is an appropriate intervention.

7. Sweet solutions

“Sweet-tasting solutions (sucrose solutions and glucose/dextrose solutions) have been extensively evaluated for their analgesic and calming effects in infants undergoing needle procedures (Harrison et al., 2012). The mechanism of action of sweet-tasting solutions is not known but may involve release of endogenous opioids and distraction. Sweet-tasting solutions are commonly used in hospital settings to reduce distress in infants undergoing various types of aversive medical procedures (Taddio, Yiu, et al., 2009; Foster et al., 2013).” (HELPinKIDS&Adults 2.0 CPG).³

Sweet-tasting solutions are usually given by syringe; however they can also be administered by dropper, cup or bottle. The effect is immediate and lasts at least five minutes which is long enough

to administer multiple injections. The upper age for the effect is unknown most studies have investigated the effectiveness of sweet-tasting solutions in the first 12 months of life.

Sucrose

Evidence: *"Eighteen studies were included in the systematic review of sucrose solutions including children in the first 19 months of life (Allen et al., 1996; Barr et al., 1995; Chattopadhyay et al., 2011; Dilli et al., 2009; Harrison et al., 2014; Hatfield, 2008; Hatfield et al., 2008a; Harrington et al., 2012; Lewindon et al., 1998; Liaw et al., 2011; Moradi et al., 2012; Mowery, 2007; Poulsen, 2009; Priambodo et al., 2008; Ramenghi et al., 2002; Sahebihagh et al., 2011; Soriano Faura & Gomez, 2003; Yilmaz et al., 2014). The sucrose concentrations evaluated ranged from 12% to 75% in all but one study, which described using a saturated solution. The volume used was 2 mL in all but three studies (others used 0.75 mL or 0.6 mL/kg) and the usual timing of administration was 1-2 minutes prior to injection. Across all distress measures (critically important outcome), the quality of evidence was high to moderate. The results were positive for 4 out of 5 measures of distress. In the analysis including the largest number of studies (n=2071 infants and children), there was a benefit for distress in the acute and recovery period combined: -0.76 (95% CI -1.19, -0.34). Sub-group analyses were undertaken for 3 of the distress outcomes; they demonstrated a dose-response relationship, with concentrations above 20% sucrose (weight/volume) appearing to be the cut-off for observable benefit."* (HELPinKIDS&Adults 2.0 CPG Recommendation 22).³

Glucose

Evidence: *"Six studies investigating glucose (dextrose) for vaccine injections including infants in the first 12 months of life were included in the systematic review (Chermont et al., 2009; Golestan et al., 2007; Goswami et al., 2013; Morelius et al., 2009; Kassab et al., 2012; Thyr et al., 2007). In included studies, the concentration of glucose ranged from 25% to 50% and the volume administered ranged from 1 - 2 mL. The timing of administration was variable: 2 minutes before injection (3 studies: Chermont et al., 2009; Golestan et al., 2007; Goswami et al., 2013), immediately before (2 studies: Kassab et al., 2012; Morelius et al., 2009), and 30 seconds before/during/10-30 seconds after (1 study: Thyr et al., 2007). There was high to moderate quality of evidence across the critical outcomes of distress; the quality was downgraded due to inconsistent blinded across studies. The results were mixed for different indicators of distress. In the only analysis that included all of the studies (n=818), there was a benefit of glucose on acute and recovery distress combined: SMD -0.69 (95% CI -1.03, -0.35)."* (HELPinKIDS&Adults 2.0 CPG Recommendation 23).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is good evidence of benefit of sweet-tasting solutions in infants not breastfed during vaccine injections. Furthermore, programs may be able to make use of rotavirus oral vaccine as the sweet-tasting solution since it contains sucrose (see Table 1 below). It is important to note, however, that the concentration of sucrose varies considerably among products available or in development and the minimal concentration that is required for analgesia is not known. At present, only one brand containing 71.5% sucrose has been demonstrated not to differ significantly in its analgesic effects compared to sucrose 24%.²⁶ Risk of dental caries and interference with breastfeeding are not considered harms as these are one-off interventions.

Table 1: Sucrose Concentrations in Different Rotavirus vaccines

	Concentration of Sucrose considered sufficient for Pain Mitigation	Concentration of Sucrose considered insufficient for Pain Mitigation
Prequalified vaccines		
GSK Rotarix™, Belgium Liquid	1.5 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 1073 mg Concentration: 71.5% 	
GSK Rotarix™, Belgium Powder		After reconstitution, 1 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 9 mg Concentration of sucrose: 0.9%
Merck RotaTeq®, USA	2 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 1080 mg Concentration: 54% 	
Vaccines in development		
Serum Institute of India – lyophilized vaccine		After reconstitution, 2.5 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 50 mg Concentration: 2%
Serum Institute of India – liquid vaccine	1 dose, 2ml contains: <ul style="list-style-type: none"> Sucrose: 568 mg Concentration: 28.4% 	
Murdoch Children's Research Institute, Australia – RV3-BB		1ml contains: <ul style="list-style-type: none"> Sucrose concentration: 10%
Biofarma, Indonesia	1 dose, 1 ml contains: <ul style="list-style-type: none"> Sucrose concentration: 30% 	
Bharat Biotech, India – ROTAVAC® licensed liquid formulation		0.5 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 37.31 mg Concentration: 7.5%
Instituto Butantan, Brazil – pentavalent rotavirus vaccine, lyophilized		0.5 ml (1 dose) contains: <ul style="list-style-type: none"> Sucrose: 30 mg Concentration: 6.0%

Resource use and value for money: Resources required include sucrose or glucose, clean water, device for administration (e.g. syringe, cup, bottle), time for preparation and training of health care workers. For these reasons, this intervention can only be conditionally recommended.

Impacts on equity: There are potential inequities if some are able to access this intervention while others are not.

Acceptability: No concerns were expressed regarding cultural acceptability. Sweet-tasting solutions are being used as a pain medicine, not as a food. It does not conflict with baby friendly initiatives.

Feasibility (implementability): This intervention would require training of health practitioners and/or caregivers. Sucrose would appear to be more feasible for people to prepare themselves or to be prepared on the spot by health care providers, but glucose is more readily available in hospital settings. Ensuring water is not contaminated would be a condition required for this intervention. However, in many parts of the world it is unlikely that all the supplies required for this intervention can be consistently and equitably procured. Sweet solutions >20% are generally effective; most commonly concentrations of 24-50% are used. There is no evidence of increased benefit with higher concentrations. One could use commercial solutions or prepare a solution with clean water (i.e., safe drinking water); in this instance use one packet of sugar (i.e. about one teaspoonful) mixed in 10 ml (i.e. two teaspoons) of water, and one should ensure that the sugar is fully dissolved, which should take no more than a couple of minutes (faster if stirred).

In places and for vaccination sessions where rotavirus vaccine is being co-administered with injectable vaccines and mothers are breast feeding, it would be best to recommend administration of the oral rotavirus, then oral polio vaccine (when OPV is used) first, then breast feeding, then injectable vaccines.

Other: Honey is not recommended as the sweet-tasting solution due to the risk of infant botulism and as per WHO guidance against feeding honey to infants <1 year of age.²⁷

8. Topical anaesthetics

“Topical anaesthetics are local anaesthetic-containing creams and gels that are applied to the skin and penetrate through the superficial layers to block transmission of nociception via Na⁺ channel blockade (McLure & Rubin, 2005). They are commonly used to treat pain from a variety of superficial skin procedures, including needle insertion, and have been demonstrated to be safe and effective in individuals of all ages, including young infants (Eidelman et al., 2005; Houck & Sethna, 2005; Taddio et al., 1998).

Health care providers, caregivers of children undergoing vaccination and adults undergoing vaccination should be instructed on the application of topical anaesthetics, including location, dose and timing. Because currently available topical anaesthetics require between 20 and 60 minutes for adequate anaesthesia, it is necessary to plan for their use. They can be administered prior to arrival at the vaccination setting or upon arrival, depending on the usual waiting times and parent and/or individual preferences.” (HELPinKIDS&Adults 2.0 CPG)³

The package instructions on how to apply these commercially produced products should be followed. Self-compounded preparations should never be used because they may either be ineffective or

dangerous (due to superficial skin irritation/damage or significant absorption through the skin and systemic toxicity).

Evidence: "Sixteen studies including individuals from infancy to adulthood were included (Abuelkheir et al., 2014; Achema et al., 2011; Basiri-Moghadam et al., 2014; Cassidy et al., 2001; Cohen et al., 1999; Cohen et al., 2006; Dilli et al., 2009; Gupta et al., 2013; Halperin et al., 2000; Halperin et al., 2002; Hansen & Sorensen, 1993; Kumar 2014; O'Brien et al., 2004; Taddio et al., 1992; Taddio et al., 1994; Uhari, 1993). The majority of included studies (n=10) investigated topical anesthetics for intramuscular vaccine injections; and remainder of the six studies investigated subcutaneous injections (n=3; Hansen & Sorensen, 1993; Halperin et al., 2002; O'Brien et al., 2004); combination of intramuscular and subcutaneous injections (n=2; Abuelkheir et al., 2014; Cohen et al., 2006) and combination of intramuscular, subcutaneous and intradermal injections (n=1; Dilli et al., 2009).

Topical anaesthetics for children up to 12 years of age

Evidence: "Fourteen studies were included in the systematic review including children in the first 12 years of life (Abuelkheir et al., 2014; Achema et al., 2011; Basiri-Moghadam et al., 2014; Cassidy et al., 2001; Cohen et al., 1999; Cohen et al., 2006; Dilli et al., 2009; Gupta et al., 2013; Halperin et al., 2000; Halperin et al., 2002; Kumar 2014; O'Brien et al., 2004; Taddio et al., 1994; Uhari, 1993). The majority of included studies were carried out in young children unable to provide self-report of pain. The quality of evidence ranged from moderate to very low. While the results were mixed for different indicators of distress, this was partly due to low sample sizes for analyses undertaken for some of the indicators and high risk of bias for some studies. In the analysis with the largest number of included studies (n=1424 children), there was a substantial benefit of topical anaesthetics on acute distress: SMD -0.91 (-1.36, -0.47). Two studies reported data for pain (Cassidy et al., 2001; Cohen et al., 1999). The quality of the evidence was moderate to very low due to risk of bias and imprecision. Without the data from one study with a high risk of bias (Cohen et al., 1999), there is high quality evidence and a benefit was observed for pain: SMD -0.47 (-0.78, -0.16). One study of very low quality included data for fear (critical outcome) for 68 children (Cohen et al., 1999). There was no evidence of a benefit of this intervention for this outcome." (HELPinKIDS&Adults 2.0 CPG Recommendation 17).³

Topical anaesthetics for adolescents >12 years and adults

Evidence: "Two studies including adolescents and adults were included in the systematic review (Hansen & Sorensen, 1993; Taddio et al., 1992). There was moderate quality evidence for the critical outcome of pain. In the single study included in the meta-analysis for critical outcomes (Taddio et al., 1992) with 60 participants, there was a benefit of the intervention: SMD -0.85 (95% CI -1.38, -0.32)." (HELPinKIDS&Adults 2.0 CPG Recommendation 18).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is good evidence of benefit. Topical anaesthetics can be used for both subcutaneous and intramuscular injections. Furthermore, up to three injections can be administered in the surface area covered by one patch. There is no evidence of an effect of topical anaesthetics on immune response to vaccines.³

A potential harm is the possibility of people self-compounding preparations, which may be ineffective or dangerous due to the risk of superficial skin damage or systemic toxicity. Therefore,

only commercially-available preparations specifically indicated for injection pain should be applied and package instructions followed.

Resource use and value for money: The cost of topical anaesthetics is a major concern. Some people in HIC and MIC may be willing and able to pay for topical anaesthetics; however this intervention is difficult or unattainable for others (especially in LIC). In some LIC, the cost of topical anaesthetic is much more than the cost of the vaccination itself.

Impacts on equity: Topical anaesthetics are not available globally, regardless of willingness to pay. In areas where they are available, there are major impacts on health equity given that some people are not able to afford this intervention. While people should have the option to avail of it, given its inequitable access around the world, the WHO cannot recommend this intervention globally.

Acceptability: There are no concerns about the acceptability of the use of topical anaesthetics. Given that vaccinations are regarded as a free health service in LIC, it would not be acceptable to recommend an intervention for which an individual would have to pay.

Feasibility (implementability): In some countries a prescription is required while in others the products are available over-the-counter. Topical anaesthetics require education to ensure proper application, as well as advanced planning and relative certainty of the time of injection given that it must be applied 20-60 minutes prior to vaccination. Health care providers administering vaccinations, caregivers of children undergoing vaccination and individuals undergoing vaccination would need to be educated about this intervention.

Other: While use should follow the product monograph, it is noted that independent studies have demonstrated that topical anaesthetics are safe and effective, even in newborn infants although the product monograph still advises that use be limited to >3 months of age. The interaction of this preparation with the immune response has been evaluated for some vaccines with no evidence of harm (i.e., no interference with antibody response). We have extrapolated their safety in this regard for all vaccines.

9. Distraction

“Distraction involves the use of strategies to divert an individual’s attention away from pain to something more pleasant. Distraction may reduce pain by engaging neural mechanisms that facilitate endogenous modulation of pain (Bandura et al., 1988; Valet et al., 2004) as well as decreasing attentional resources that would otherwise be allocated to processing of pain (Johnson, 2005). There may be substantial individual differences in the effectiveness of distraction for pain reduction (Van Damme et al., 2010). Distraction may be more effective for individuals whose typical coping style involves disengaging (Verhoeven et al., 2012; Piira et al., 2006; Fanurik et al., 1993) rather than attending to the source of pain and also for those who have a low fear of pain (Roelofs et al., 2004).

Distraction can be achieved using a variety of ‘distractors’. In children, this typically includes toys, videos, and music. However, distraction can also involve conversation with an adult. Distractors that are very engaging, interactive, and intrinsically interesting are believed to be more effective (Cohen 2008). Distraction is typically commenced before the procedure begins, and is continued during and afterwards - this is believed to reduce anticipatory anxiety, pain, and to enhance recovery, respectively (Cohen 2008). Recent systematic reviews demonstrate some benefit of distraction for reducing pain during needle procedures, including vaccination, in children (Birnie et al., 2014; Pillai Riddell et al., 2014; Uman et al., 2013).

In general, the ability to intentionally and capably engage in self-regulatory processes improves with age and individuals become less reliant on external sources (e.g., distractors) to cope with pain (Skinner & Zimmer-Gembeck, 2007). Adults may be more likely to engage in cognitive distraction, in which they can distract themselves effectively merely by thinking about other things.” (HELPinKIDS&Adults 2.0 CPG).³

The distractions examined for these global recommendations included music, videos, toys, breathing interventions, verbal and visual distraction.

Toys: for infants and very young children (up to 3 years)

Evidence: “Five studies including 549 children aged 2 months to 3 years were included in the systematic review that investigated directed toy distraction (Cramer-Berness 2005; Cramer-Berness & Friedman, 2005a; Gedam et al., 2013; Hillgrove-Stuart et al., 2013; Singh, 2012). In three of them, parents were instructed in distraction. There was low to very low quality evidence across the critical outcomes of distress due to risk of bias with or without imprecision. The results were mixed; a benefit was demonstrated for distress pre-procedure, acute and recovery combined in one study [n=81; SMD -0.47 (95% CI -0.91, -0.02)]. In the only analysis that included all 5 studies (n=549), there was no evidence of a benefit for acute distress: SMD -0.94 (95% CI -1.98, 0.10). (HELPinKIDS&Adults 2.0 CPG Recommendation 33).³

Four studies including children aged 2 months to 3 years were included in the systematic review that investigated non-directed toy distraction (Basiri-Moghadam 2014; Cramer-Berness, 2005; Ozdemir & Tufekci 2012; Singh, 2012). The methods of distraction included toys and mobiles. There was low to very low quality of evidence due to risk of bias and imprecision for the critical outcome (distress) and the results were mixed for different indicators of distress. In the only analysis that included all 4 studies (n=290), there was a benefit for acute distress: SMD -0.93 (95% CI -1.86, 0.00). (HELPinKIDS&Adults 2.0 CPG Recommendation 34).³

The evidence base for toy distraction in children > 3-12 years is presented under Breathing Interventions (below).

Music: For children >3-12 years

Evidence: “Four studies including children aged 3 to 7 years were included in the systematic review (Fowler-Kerry & Lander, 1987; Megel et al., 1998; Noguchi, 2006; Yinger 2012). There was low quality evidence due to risk of bias and imprecision. There was evidence of a benefit for pain: in the analysis including all the largest number of studies (n=361), the SMD was -0.45 (95% CI -0.71, -0.18). There was no evidence for the critical outcome of fear.” (HELPinKIDS&Adults 2.0 CPG Recommendation 37).³

Music: For adolescents >12-17 years

Evidence: “One study including adolescents 13 to 15 years was included in the systematic review (Kristjánsdóttir & Kristjánsdóttir, 2011). There was low quality evidence due to risk of bias and no evidence of a benefit: [(n=118): SMD -0.04 (95% CI -0.42, 0.34). There was no evidence for the critical outcome of fear.” ((HELPinKIDS&Adults 2.0 CPG Recommendation 38).³

Music: For Adults

Evidence: *“No studies were identified specific to vaccine injections. Two studies including 156 adults undergoing venipuncture were included in the systematic review (Jacobson, 1999; Jacobson, 2006). In both studies, individuals self-selected from a variety of options. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for both critical outcomes.” (HELPinKIDS&Adults 2.0 CPG Recommendation 39).*³

Video: For infants and very young children (up to 3 years)

Evidence: *“Four studies including 512 children aged 1 month to 3 years were included in the systematic review (Cohen, 2002; Cohen, Bernard et al., 2006; Cohen, MacLaren et al., 2006a; Gedam et al., 2013). In three of the studies, nurse immunizers were instructed in distraction prior to commencement of the study (Cohen, 2002; Cohen, Bernard et al., 2006; Cohen, MacLaren et al., 2006a) and in one of the studies, parents were also instructed in distraction (Cohen, MacLaren et al., 2006a). In all included studies, children were encouraged to engage in the distraction. There was moderate to very low quality evidence for the critical outcomes of distress due to imprecision +/- risk of bias. The results were mixed; there was evidence of a benefit for pre-procedural distress [(n=216); SMD -0.49 (95% CI -0.76, -0.22)] and distress acute and recovery combined [(n=126); SMD -0.68 (95% CI -1.04, -0.32)]. In the analysis including the largest number of studies (n=456), there was no evidence of a benefit for acute distress: SMD -0.63 (95% CI -1.53, 0.27).” (HELPinKIDS&Adults 2.0 CPG Recommendation 32).*³

Video: For Children >3-12 years

Evidence: *“Five studies including children aged 2 to 12 years were included in the systematic review (Cassidy et al., 2002; Cohen et al., 1997; Cohen et al., 1999; Cohen et al., 2015; Luthy et al., 2013). Nurse immunizers, parents and/or children received verbal, written or video instruction in distraction in 2 of the studies (Cohen et al., 1997, Cohen et al., 1999) and children typically watched a cartoon or movie on a television. There was very low quality evidence for critical outcomes (pain and fear) due to risk of bias and imprecision. There is no evidence of a benefit for pain or fear. When the single study that allowed the child to choose from several available videos (Cohen et al., 1997) was examined separately, a benefit of video distraction was observed for pain. There was very low quality of evidence for distress (important outcome) and evidence of a benefit across all 3 indicators assessed. In the analysis including all 5 studies (n=327), the SMD was -0.96 (95% CI -1.85, -0.08).” (HELPinKIDS&Adults 2.0 CPG Recommendation 36).*³

Verbal Distraction: For Children >3-12 years

Evidence: *“Two studies on parental verbal distraction including 46 children aged 3 to 7 years were included in the systematic review (Gonzalez et al., 1993; O’Laughlin & Ridley-Johnson, 1995). Parents were instructed either by using a pamphlet, or by oral instruction plus listening to a tape and practicing. Parents then distracted their child by talking to them, counting, singing, discussing other objects in the room, reciting a poem/rhyme, or other. There were no studies that examined verbal distraction provided by a clinician. There was low quality evidence due to risk of bias and imprecision for one of the critical outcomes (pain) and no evidence for the other (fear). There was no evidence of a benefit on pain. Given the young age range of the participants and that self-report may have been*

challenging (Chambers & Johnston, 2002; von Baeyer, Forsyth et al., 2009), we also examined distress; there was low quality of evidence for distress (important outcome) and evidence of a benefit for the analysis that included both studies: SMD -1.22 (95% CI -1.87, -0.58).” (HELPinKIDS&Adults 2.0 CPG Recommendation 35).³

Visual Distraction: For Adults

Evidence: “No studies were identified specific to vaccine injections. Two studies including adults undergoing venipuncture were included in the systematic review (Cason & Grissom, 1997; Jacobson, 2006). A kaleidoscope was used as the distractor in both studies. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias, indirectness and imprecision and no evidence of a benefit for both critical outcomes.” (HELPinKIDS&Adults 2.0 CPG Recommendation 40).³

Breathing interventions

“Breathing interventions have been proposed to reduce pain and fear during medical procedures. A variety of techniques have been studied, including; deep breathing or blowing, coughing, forceful breath-holding or exhalation. Breathing facilitated with toy distractors typically includes bubbles or pinwheels. Deep breathing (i.e., belly or diaphragmatic breathing) which causes body relaxation, is often included in cognitive-behavioural treatments for pain (Benson, 1975; Schaffer & Yucha, 2004; Uman et al., 2013); however, it is unclear to what degree it was incorporated in the reviewed studies.” (HELPinKIDS&Adults 2.0 CPG).³

Breathing with a toy distraction (e.g., blowing bubbles, pinwheels): For Children >3-12 years

Evidence: “Six studies including 368 children aged 3 to 9 years were included in the systematic review (Beran et al., 2013; Blount et al., 1992; Bowen & Dammeyer, 1999; Krauss, 1997; Manimala et al., 2000; Sparks, 2001). In three of them, parents and children received instruction prior to the procedure. A variety of props were used to facilitate breathing, including: bubbles, pinwheels, and responding to a robot’s request to blow dust off a toy. There was very low quality evidence for critical outcomes (pain, fear) due to risk of bias and imprecision. There was evidence of a benefit for pain [$n=123$; SMD -0.49 (95% CI -0.85, -0.13)]. There was no evidence of a benefit for fear. There was very low quality of evidence for distress (important outcome). In the analysis including the largest number of studies ($n=222$ participants), there was evidence of a benefit for pre-procedure, acute and recovery distress combined: SMD -0.55 (95% CI -0.82, -0.28).” (HELPinKIDS&Adults 2.0 CPG Recommendation 41).³

Breathing without a toy distraction (deep breathing, blowing): For Children >3-12 years

Evidence: “Two studies including 136 children aged 3 to 7 years were included in the systematic review (Cohen et al., 2002; French et al., 1994). In both studies, children were instructed in breathing exercises prior to vaccinations. In one study (Cohen et al., 2002), children watched a video introducing “snake breathing” where they are instructed to breathe deeply with a hissing sound. Introducing breathing in this way may have helped to make the strategy more concrete/clear and interesting; however, it was also potentially fear-inducing. The video also taught children about positive self-statements (i.e., “I am cool and calm”) and showed a child modelling these strategies. In the second study (French et al., 1994), children were instructed to take a deep breath and blow and

blow and blow until they were told to stop. There was very low quality evidence for critical outcomes (pain and fear) due to risk of bias and imprecision and no evidence of a benefit. There was very low quality of evidence for distress (important outcome) and no evidence of a benefit.” (HELPinKIDS&Adults 2.0 CPG Recommendation 42).³

Breathing Interventions (cough): Children >3-17 years

Evidence: “One study including 136 children 4 to 13 years was included in the systematic review (Wallace et al., 2010). Children were asked to cough during vaccination. There was low quality evidence due to risk of bias and imprecision. There was no evidence of a benefit on pain, one of the critical outcomes and no data for fear, the other critical outcome.” (HELPinKIDS&Adults 2.0 CPG Recommendation 43).³

Breathing Interventions (cough, breath-hold): Adults

Evidence: “No studies were identified specific to vaccine injections. Two studies including 138 adults undergoing venipuncture were included in the systematic review (Basaranaglu 2006, Usichenko 2004). In one study, participants coughed during the procedure. In the other, participants were asked to perform a deep inspiration and then breath-hold. There was very low quality evidence for the critical outcome of pain due to risk of bias, indirectness and imprecision. There was evidence of a benefit for pain: SMD -0.82 (95% CI -1.21, -0.43). There was no evidence for the critical outcome of fear.” (HELPinKIDS&Adults 2.0 CPG Recommendation 44).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is some evidence of benefit of different distractors in different ages: toys and videos in young children 0-3 years; music, videos, verbal distraction, and toys with breathing in children >3-12 years; and breathing interventions in adults. Some individuals may prefer to attend to the procedure as that is their style for coping and this should be taken into consideration when using distraction (as per below under acceptability).

Resource use and value for money: Distraction requires tools such as music players, video screens and toys which may not be procurable in LMIC. Breathing interventions evaluated for adults require no additional tools.

Impacts on equity: There are potential inequities for music, videos, breathing with a toy if some are able to access this intervention while others are not. There is no inequity with use of breathing interventions for adults.

Acceptability: Child and adult characteristics need to be considered: The effectiveness of distraction depends on intrapersonal and interpersonal variables and the attributes of the distractor. For example, distraction may be less effective or even may have counterproductive effects in individuals who perceive pain as highly threatening (i.e., have high levels of catastrophizing or worrisome thoughts about pain.^{28,29,30} Breathing interventions are expected to be acceptable for adults.

Feasibility (implementability): Music may be the most feasible distraction as it is the most accessible globally. Although no studies have been conducted on the effectiveness of singing it is likely to work. Other distractions such as videos and toys may be possible depending on context. The results of

distraction interventions are highly variable (as described above) and there are concerns about fidelity of the intervention. For adults, breathing interventions are feasible although minor teaching may be required, which can be accomplished during the vaccination episode.

Other: Many distraction techniques have limited evidence and variable effectiveness. In children, youth, and adults, the universally effective intervention is topical anaesthetics. If topical anaesthetics are not affordable or accessible, we need to optimize the distraction intervention.

10. Oral analgesics

“Acetaminophen and ibuprofen are analgesics commonly administered in children and adults to treat fever and pain. They have been used in the context of vaccination in order to prevent and abort vaccine-induced fever and ‘delayed’ pain (i.e., occurring hours to days after vaccination) (Manley & Taddio, 2007). There is some controversy regarding their routine use to prevent and/or treat side effects of vaccination because of the potential to interfere with the immune response of some vaccines (Prymula et al., 2009). For the purposes of this guideline, a summary of the research evidence regarding the effectiveness of acetaminophen and ibuprofen specifically for reducing acute pain (rather than delayed pain) during vaccine injections was reviewed.” (HELPinKIDS&Adults 2.0 CPG).³

Evidence: *“No studies specific to mitigation of pain at vaccine injections were identified. One study including children aged 1 to 18 years with cancer undergoing needle insertion into a subcutaneously implanted port was included in the systematic review (Hedén et al., 2014). Children received either acetaminophen (40mg/kg) or placebo 1 hour prior to port access. There is low quality evidence for pain (critical outcome) due to indirectness and imprecision and no evidence of a benefit from this intervention.*

Five studies were identified that examined the potential for interference with the immune response with acetaminophen use prior to vaccination. Three studies including 442 adults receiving influenza vaccine demonstrated no difference in the immune response for those who received acetaminophen compared to placebo (Aoki et al., 1993; Chernesky et al., 1993; Gross et al., 1994). In one study including 496 health care workers receiving hepatitis B vaccination series, a 26% reduction in hepatitis surface antigen antibodies was observed in the acetaminophen group (Doédee et al., 2014). Similarly, in one longitudinal study including 459 healthy infants following their primary and booster vaccination (10-valent pneumococcal non-typeable Haemophilus influenza protein D-conjugate vaccine, diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type b vaccine and rotavirus vaccine), lower levels for all 10 pneumococcal vaccine serotypes, protein D, anti-diphtheria, anti-tetanus and anti-pertactin was observed in the prophylactic acetaminophen group (Prymula et al., 2009). The proposed mechanism for reduced immunogenicity is interference with the early interactions of the dendritic cells, T cells and B cells of the primary immune response to conjugate and toxoid vaccines via reduction of inflammatory signals at the injection site (Prymula et al., 2009).” (HELPinKIDS&Adults 2.0 CPG Recommendation 20).³

With regard to ibuprofen, *“No studies specific to vaccine injections were identified. One crossover trial including 10 adult volunteers undergoing venipuncture was included in the systematic review (Smith et al., 1996). Adults received ibuprofen 5% cream and lidocaine-prilocaine 5% cream 1 hour prior to venipuncture. There is very low quality evidence for pain (critical outcome) due to*

indirectness (procedure, route of administration of ibuprofen, and active comparison group) and imprecision. Pain scores were higher for the ibuprofen group compared to lidocaine-prilocaine 5%.

No studies were identified that evaluated the effect of ibuprofen on vaccination antibody response. Ibuprofen is an inhibitor of the cyclooxygenase enzyme and it is unclear whether blocking the metabolites of this enzyme system will interfere with vaccine effectiveness (Chen et al., 2009).” (HELPinKIDS&Adults 2.0 CPG Recommendation 21).³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and Harms: Due to the lack of evidence of clear benefits and the potential for harms in terms of reducing efficacy of vaccines, oral analgesics were not recommended by the technical consultation group for pain mitigation at the time of injection. Oral analgesics can still be used in an individual context to mitigate the fever and local pain that may be experienced post vaccination.

Other interventions reviewed and not recommended for global use and included in HELPinKIDS&Adults 2.0 CPG Recommendation - See Appendix 2

- Non-nutritive sucking
- Simultaneous injections
- Manual tactile stimulation
- Warming the vaccine
- Vapocoolants

Other interventions for which the evidence is NOT presented in this document but included in HELPinKIDS&Adults 2.0 CPG³

- Muscle to be injected
- Muscle tension to decrease fainting
- Tactile stimulation using vibration and cold
- Skin to skin contact in neonates
- Strategies to address individuals with high levels of needle fear

Education of clinicians, children, adults and caregivers

Evidence presented during the consultation and *Evidence to Decision Elements of GRADE_DECIDE framework* are provided in **Appendix 3** as it was agreed that these should not be seen as separate interventions but part of the implementation process for recommended interventions.

Interventions for which there is no evidence

The technical consultation group considered a number of interventions for which there is no evidence for reducing pain or distress, including:

- effects of changing the needle after drawing the vaccination solution;
- effects of looking at versus away from the needle during injection; and
- effects of the setting in which vaccination occurs, such as whether being immunized in private or with many people has an effect on pain.

Due to a lack of evidence, these interventions are not currently recommended. Of note changing the needle could not be an alternative in the context of WHO's policy on the exclusive of auto-disable syringes for immunization as the specification for those syringes include the fact that the needle cannot be detached from the syringe.

Consultation with industry

Efforts were made to solicit industry's input through both the International Federation of Pharmaceutical Manufacturers & Associations and the Developing Countries Vaccine Manufacturers Network. During the technical consultation, a representative from a vaccine manufacturing company was invited to share information about ongoing efforts/initiatives the vaccine industry is undertaking/pursuing to address the issue of acute pain during vaccination. The representative informed the group of the following:

- Manufacturers evaluate the safety and tolerability of the vaccines licensed or in development assessing local reactions including pain as requires by the regulatory agencies, but they do not specifically evaluate pain at time of injection
- No known manufacturers are systematically collecting data on pain during injection
- Manufacturers recognize that pain correlates with vaccination schedules (e.g. multiple injections), and understand that pain and fear of injections influence vaccine hesitancy
- There are no known current activities/ongoing initiatives on reducing pain during vaccination

Group members posed the following questions to the industry representative:

- Could pain at the time of vaccination be measured as part of vaccine development (e.g. chemicals chosen, pH, isotonicity)? This is important since one of our recommendations is to inject the most painful vaccine last, and in order to do so we need an objective method of rating the painfulness of different vaccines.
- Could pain at the time of vaccination be included as an endpoint during formulation and early trials, and captured on case report forms? Could manufacturers be made obligated to collect this data if regulatory bodies made it a licensing requirement and the pain at time of vaccination profile be included in the package insert?
- Could advice be included in package insert to vaccine administrators on how to reduce pain, which would have to go through the regulators?
- Could different manufacturers be incentivized to collaborate to develop less painful vaccines and combination vaccines?

Consultation with National Immunization Managers in Africa (implementability survey)

Participants: Twenty-five managers from 25 different African countries participated in an implementability of intervention survey. These surveys took place at two sub-regional African Immunization managers meetings, one Francophone and one Anglophone.

Methods: Each participant was provided with questions and four exemplar recommendations [1. Do NOT aspirate when giving vaccines to all ages (strong recommendation), 2. Administer vaccines from the least to the most painful vaccine for all ages (strong recommendation), 3. Breastfeed at time of immunizations for infants (conditional recommendation: for women who are breastfeeding and for whom breastfeeding during the vaccination session is culturally acceptable in the vaccination setting), 4. Use neutral words at the time of vaccination; avoid language that increases anxiety (strong recommendation) for all ages as examples and asked to respond to a written survey on a series of evidence to decision implementation questions. The responses are summarized below in connection with the questions asked and the complete responses appear in **Appendix 4**.

1. Are there cultural or gender dimensions that might impact on the implementation of these recommendations? Responses: No issues reported by majority of participants, but sometimes breastfeeding identified as a potential issue
2. How might the patient's values and preferences impact the implementation of these recommendations? Response: Parents most concerned about pain, and post vaccination pain where they may want medications, but influenced by knowledge, attitudes and previous experience of vaccinations. Recommendations predicted to be positively viewed by parents and could lead to higher acceptance of vaccines.
3. How feasible will it be to train health care workers and implement these recommendations? Response: Feasible commonly reported, suggestions for Train of trainers, but Ministry of Health training needs updates, need formative training and supervision, need theory and practical training.
4. What do you see as some of the main barriers from the health care worker perspective? Response: Poor knowledge and noncompliance of workers- training needed, stopping aspiration, long history of neglecting pain, some workers mirror the child's reaction- i.e. crying with child so this will may be difficult to change.
5. Do you believe health care workers will accept these new recommendations? Response: Most commonly reported as acceptable, but may need to convince workers that pain is unacceptable, you need to explain and follow-up.
6. What recommendations are most likely not to be followed early on? Response: Variable-dependent on what recommendations already being done in practice and training- see Appendix 4.
7. What recommendations do you feel are most likely to be followed early on? Response: Variable-depending on what is already being done in practice and training- see Appendix 4.
8. What do you feel will be the cost of the time, training, and implementation of these recommendations? Response: Minimal cost commonly reported, best to integrate with existing training and training for new vaccines: plan cascade of training from national to district levels.

Conclusions: There was consistency among the 25 African immunization managers: culture and gender were not concerns, with the rare exception of certain women who may be reluctant to breastfeed in a public clinic. Parents are concerned about pain and so these proactive recommendations will be well received and may improve acceptance of vaccine. The new recommendations are feasible but training will be needed. Main obstacles centred on previous practice (aspiration), conducive conditions for breastfeeding, training workers to understand and value pain prevention recommendation. Virtually all predicted acceptability for recommendations, but there was some variation, depending on local practice, as to which recommendations would be most easily implemented.

Limitations and additional notes

- The evidence on the effectiveness and safety of interventions, while coming from all regions (see Figure 1), predominately came from the region of the Americas and the European region and from High Income Countries.
- The evidence was limited to what had been included in HELPinKIDS&Adults 2.0 CPG.
- The HELPinKIDS&Adults 2.0 CPG used a strict approach in using GRADE that often resulted in reporting high levels of uncertainty of evidence.
- The evidence base for many interventions did not cover all the age groups of interest thus requiring extrapolation for recommendations. Attention to WHO age categorization and related immunization programs will be important in the future.
- Psychological interventions maybe very operator dependent as well as having inter-subject variability e.g. distraction.
- Trials that examined multiple pain mitigation strategies being used at the same time were not included; in many cases, however, co-interventions could have occurred: e.g. breastfeeding at same time as most painful injected last. Combining effective interventions may improve pain relief beyond individual interventions.
- Many of the trials were done in clinical settings that are not reflective of the range of environmental conditions in LMIC.
- Complex psychological interventions such as hypnosis were excluded as impractical.
- Intramuscular versus subcutaneous administration for vaccines was not assessed due to the scanty evidence base and the potential to make recommendations that may disagree with the manufacturer's approved route.
- Complementary and alternative medicine was excluded.
- Given that pain in general is not well addressed in low resource settings³¹ there is a need to draw attention to pain mitigation at the time of vaccination. This may increase awareness about pain in other contexts and improve the quality of care delivered across the health care continuum.

Future research questions

The group identified gaps in the literature that would be useful for informing future recommendations on reducing pain during vaccination. The following questions were prioritized from a larger list for research from a global perspective:

- Is there a difference in pain on injection between delivering intramuscularly or subcutaneously for vaccines that are licensed for administration by either route e.g. measles-containing vaccines?
- What distractions, in the ages where applicable, are effective and implementable?
 - Which distractions are appropriate in different geographical contexts and income settings?
 - How should distractions be administered?
- Is there any difference in pain on injection when using multiple injections in one limb or multiple limbs?
- What interventions to reduce pain during vaccination are effective in mass campaigns and school-based programs?
 - What environmental interventions are effective (e.g. privacy, visual cues)?
- Other research questions not prioritized:
 - Can additional head-to-head studies and add-on studies be conducted to determine the relative effectiveness of different interventions and the additive effects of interventions?
 - Can additional studies be conducted to determine how parents and individuals undergoing vaccination in different contexts want to learn about preventing pain at the time of vaccination? This will help identify proper health promotion avenues that could help strengthen other health care messages as well.

Conclusions

Pain and distress at the time of vaccination is an important clinical issue for individuals of all ages undergoing vaccination, their caregivers and health care providers administering vaccinations. Not addressing pain at the time of vaccination can engender vaccine hesitancy and may impact on future health seeking behaviour and health care decisions. There are evidence based strategies to mitigate pain at the time of vaccination that are feasible, culturally acceptable and can be applied in high, middle and low income countries. Addressing pain and distress at the time of vaccination is especially important for young and school-age children who are at highest risk of the adverse sequelae of untreated pain (i.e., development of needle fears and long-term negative attitudes and non-compliant behaviours). For infants, young and school aged children, a more comprehensive approach is recommended due to the high levels of distress associated with vaccine injections and potential for long-term harm of unmitigated pain. When sufficiently mature and able to give their preferences, a more self-directed and individualized approach can be used. As the relief of pain during health-related procedures is also accepted as a basic human right, mitigation of pain at vaccination should be part of good vaccination practice around the globe.

Recommendations and implementation

Interventions for reducing pain, distress and fear at the time of vaccination

The following are interventions (recommended and not recommended) for reducing pain, distress and fear during vaccination, categorized by age:

All ages	
Recommended for national programmes	Not recommended for national programmes as routine practice
<ul style="list-style-type: none"> • No aspiration • Administer vaccines in order of increasing painfulness • Proper positioning • Use of neutral words; avoiding language that increases anxiety and/or promotes distrust 	<p><u>Effective but not practical*</u></p> <ul style="list-style-type: none"> • Topical anaesthetic <p><u>Unknown effectiveness:</u></p> <ul style="list-style-type: none"> • Changing the needle • Looking at vs. away from needle • Organizational aspects of the setting: privacy, environment <p><u>Ineffective:</u></p> <ul style="list-style-type: none"> • Manual stimulation <p><u>Ineffective with potential harms:</u></p> <ul style="list-style-type: none"> • Oral analgesics • Warming the vaccine

Infants	
Recommended for national programmes	Not recommended for national programmes as routine practice
<ul style="list-style-type: none"> • Caregiver presence <p><u>Conditional recommendations:</u></p> <ul style="list-style-type: none"> • Breastfeeding • Administration of sweet solutions if breastfeeding not acceptable during the vaccination session or shortly before (including rotavirus vaccine) 	<p><u>Effective but not practical:</u></p> <ul style="list-style-type: none"> • Pacifiers and finger/thumb sucking • Simultaneous injections <p><u>Equivocal effectiveness and impractical</u></p> <ul style="list-style-type: none"> • Distraction <p><u>Ineffective:</u></p> <ul style="list-style-type: none"> • Vapocoolants

Children	
Recommended for national programmes	Not recommended for national programmes as routine practice
<ul style="list-style-type: none"> • Caregiver presence <p><u>Conditional recommendations:</u></p> <ul style="list-style-type: none"> • Distraction (e.g. Music) 	<p><u>Ineffective:</u></p> <ul style="list-style-type: none"> • Vapocoolants

Adolescents and Adults (including pregnant and breastfeeding women)	
Recommended for national programmes	Not recommended for national programmes as routine practice
<u>Conditional recommendations:</u> <ul style="list-style-type: none"> Distraction (no evidence that effective in adolescents) <ul style="list-style-type: none"> Breathing interventions (cough, breath-hold) 	<u>Equivocal effectiveness and not practical:</u> <ul style="list-style-type: none"> Vapocoolants (no evidence that effective in adolescents) <u>Ineffective:</u> <ul style="list-style-type: none"> Visual distraction Music distraction

*practicality encompasses cost, feasibility and acceptability

Recommendations to WHO

The technical consultation group recommends the following to WHO in consideration of implementation of the above interventions:

- Ensure alignment of guidance documents or statements posted on the web with the above mentioned recommendations.
- Include pain mitigation recommendations within WHO immunization materials.
- Align pain mitigation recommendations with other departments and policies² e.g. breastfeeding, pacifiers, rotavirus vaccine, aspiration, etc.
- Disseminate pain/fear mitigation recommendations through SAGE report and its usual dissemination channels, Expanded Programme on Immunization (EPI) managers, National Immunization Technical Advisory Group (NITAG) members and partners.
- Consider publication of a specific self-standing guidance document or inclusion with other immunization practice guidance.
- Complete the training modules for mid-level immunization managers (MLM) with respect to interventions to reduce pain at the time of the vaccination event.
- Monitor and evaluate implementation success of pain mitigation measures.
- Encourage/promote generation of data on immediate pain at the time of vaccination during vaccine development and Adverse Event Following Immunization (AEFI) reporting.⁴
- Work with the Expert Committee on Biological Standardization (ECBS) and regulatory agencies to advocate that grading of pain experienced during the vaccination event be included in data for licensing and in the product monograph.

Recommendations to countries

The technical consultation group recommends the following to countries in consideration of implementation of the above interventions:

- At the health system level:
 - Strengthen health policy by:
 - Including the mitigation of vaccination pain and fear at the time of injection as part of good vaccination practice, and
 - Recognizing pain and fear at the time of injection as distinct from other pain adverse events and as one factor in selection of a vaccine.
 - Support and monitor implementation success (ICC/NITAG).

- Integrate recommendations into immunization programs by:
 - Providing preferred order of injection for country-specific vaccination schedules
- Include vaccine pain mitigation in health care worker curriculae.
- Through education of health care workers and pre-service workers, and continuing education:
 - Ensure understanding and appreciation of pain and fear with vaccination injection.
 - Include the following content:
 - Assessment of pain and fear during the time of vaccination; and
 - Mitigation of pain and fear at the time of vaccination, including interventions such as
 - No aspiration,
 - Using the most painful injection last,
 - Positioning,
 - Language and interaction, and
 - Other interventions tailored to age-specific groups such as breast feeding for infants.
- Through education of caregivers, and those receiving vaccines who are old enough to be educated (adults, older children, youth) :
 - Include education on vaccination pain mitigation:
 - during pre-natal visits,
 - with breastfeeding education, and
 - at the time of vaccination.
 - Methods of education could include pamphlets, one-on-one or group verbal instruction, posters, and other techniques.

Appendix 1: Declaration of Interests

All eight experts participating in the 16-17 February 2015 Technical Consultation completed a declaration of interests. Two experts reported relevant interests that are summarized below. All interests were assessed not to constitute a conflict of interest in regard to serving on the Technical Consultation. It was concluded that all members could take part in full in all of the discussions.

Professor Anna Taddio

- Received an investigator-initiated grant from Pfizer (2011-2015) for a longitudinal randomized controlled trial investigating the effectiveness of parent-led interventions in reducing infant hypersensitivity to pain. This interest was assessed as non-personal, specific and financially significant.*
- Received supplies from Natus³² and Ferndale³³ in relation to research on reducing vaccine injection pain. These interests were assessed as non-personal, specific and financially significant.*

Professor Christine Chambers

- Provides occasional consulting to AbbVie³⁴ on topics such as pain management and needle fears in persons living with inflammatory bowel disease. This interest was assessed as personal, specific and financially significant.*

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a "significant shareholding".

Appendix 2: Other HELPinKIDS&Adults 2.0 CPG Recommendation interventions reviewed and not recommended for global use

1. Non-nutritive sucking

“Non-nutritive sucking is defined as sucking not relating to or providing nutrition and is recognized for its pacifying effects in infants (Jenik & Vain, 2009). Non-nutritive sucking can be achieved using a variety of methods, including finger/thumb or an external device (pacifier/soother). Non-nutritive sucking has been the subject of much research and controversy regarding its potential effects, both negative and positive (reviewed in Nelson 2012). For the purposes of this guideline, a summary of the research evidence regarding its effectiveness specifically for reducing distress during vaccine injections was reviewed. The mechanism of action of non-nutritive sucking in this context, while not known, has been hypothesized to involve the activation of orotactile and mechanoreceptors, which may inhibit nociception or provide distraction (McNair et al., 2013). There is evidence for the efficacy of non-nutritive sucking for procedural pain management in neonates (Pillai Riddell et al., 2011).” (HELPinKIDS&Adults 2.0 CPG).³

Evidence: *“Two studies including infants from 0-4 months of age were included in the systematic review (Liaw et al., 2011; Taavoni et al., 2010a). There was low to very low quality of evidence across the different outcomes of distress (critical outcome) due to risk of bias and imprecision and evidence of a benefit of the intervention. In the only analysis that contains data from both studies (n=186), the SMD was -1.88 (-2.57, -1.18) for acute distress. The rate of sucking may be important for effectiveness; included studies did not determine sucking rate.” (HELPinKIDS&Adults 2.0 CPG Recommendation 12).³*

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is evidence of benefit with non-nutritive sucking. However, finger/thumb sucking may not occur spontaneously at the time needed. WHO advises against the use of pacifiers for breastfeeding infants.³⁵

Resource use and value for money: For infants that suck their own thumbs or that use a pacifier, no additional resources are needed. It is unlikely that health care facilities would supply pacifiers for the sole purpose of mitigating vaccination pain. An adult may be required to hold the pacifier in place to stimulate sucking and prevent the device from falling out of the infant’s mouth.

Impacts on equity: This intervention with a pacifier may be inequitable if some have access to pacifiers and others do not.

Acceptability: Pacifiers are not available or used globally. Sucking on finger/thumb is acceptable in young infants but may not occur at time needed.

Feasibility (implementability): It is not feasible for infants who do not regularly use pacifiers to begin solely for the purpose of reducing pain during vaccination and finger/thumb sucking does not always occur spontaneously at the moment needed.

Other: None

2. Simultaneous injections

“At present, immunization schedules commonly recommend more than one separate vaccine injection at a single visit. There is the possibility to inject multiple vaccines simultaneously rather than sequentially. On the one hand, rapid administration of both injections at once may help reduce pain due to sensitization (i.e., increase in pain intensity over time due to repeated nociceptive stimulation) and less anticipatory distress. In contrast, some children might find it alarming to be approached by more than one individual with a needle at once. The potential for differences in how this intervention might work across childhood due to differences in the factors described above led us to examine the effects of this intervention for infants and children separately.” (HELPinKIDS&Adults 2.0 CPG).³

Simultaneous injection: In Infants (<1 yr)

Evidence: *“Two studies including infants aged 2 to 6 months were included in the systematic review (Hanson et al., 2010; McGowan et al., 2013). There was low quality evidence for distress (critical outcome) due to risk of bias and imprecision. The results were mixed for different indicators of distress. In the only analysis that included data from both studies (n=172), acute distress was lower in the infants in the simultaneous injection group: SMD -0.56 (-0.87, -0.25). There were no identified undesirable consequences to the infant although this has not been well studied.” (HELPinKIDS&Adults 2.0 CPG Recommendation 3).³*

Simultaneous Injection: In children 1- 10 years

Evidence: *“One study including children aged 4 to 6 years was included in the systematic review (Horn et al., 1999). There was very low quality evidence for pain (critical outcome), primarily due to high risk of bias (lack of blinding and standardization of procedures, imbalance in baseline characteristics of study groups) and low sample size (n=44 included in analysis). There was no evidence of a benefit of this intervention. Having two clinicians present to administer vaccine injections simultaneously may increase child fear. There may also be alterations in positioning of children and restraining of children to ensure that simultaneous injections can be administered safely, which can further increase fear.” (HELPinKIDS&Adults 2.0 CPG Recommendation 4).³*

Conclusions

Though there is evidence of benefit for this intervention in infants but not in children, consistent availability of multiple immunizers was not considered feasible in many high, middle or low-income settings. Therefore, this intervention was considered effective in infants but not practical and was not discussed in detail.

3. Manual tactile stimulation

“Stimulation of the skin (tactile stimulation) adjacent to the site of a simultaneously occurring painful medical procedure or on the contralateral side by manually rubbing, stroking or applying pressure or applying a vibrating device has been evaluated to reduce pain from needle procedures. The proposed mechanism of action involves the gate control theory of pain and the notion that the touch sensation competes with the pain sensation to reduce the pain signal to the brain (Wall 1978).” (HELPinKIDS&Adults 2.0 CPG).³

Evidence: “Six studies including individuals from infancy until adulthood were included in the systematic review (Chung et al., 2002; Hogan, Probst et al., 2014; Jose & Shetty, 2012; Nakashima et al., 2013; Sparks, 2001; Taddio, Ho et al., 2014a). There was moderate to very low quality evidence for critical outcomes (pain and distress), in part due to high risk of bias, inconsistency and imprecision. There was no evidence of a benefit for pain (n=893): SMD -0.38 (95% CI -0.96, 0.21). Similarly, there was no evidence of a benefit for any indicator of distress. In the analysis of acute distress that included all the relevant studies (n=301 participants), the SMD -0.69 (-1.77, 0.39). The evidence base includes heterogeneity in the delivery of the intervention, type of injection, and co-interventions. Aspects of the intervention and the process of administering vaccines used in the trials (e.g., pinching the skin or securing the limb) may have introduced contamination that offset the benefit of this intervention.” (HELPinKIDS&Adults 2.0 CPG Recommendation 13).³

Conclusions

As there is evidence that this intervention is ineffective, a recommendation against manual stimulation was made by the technical consultation group.

4. Warming the vaccine

“Injectable medications which deviate from normal body temperature in either direction may activate nociceptors, leading to the sensation of pain. Altering the temperature of medications has therefore been undertaken to try to counter the potential pain-inducing effects. With respect to vaccines, they are usually refrigerated and their cold temperature may contribute to the pain experienced by individuals during administration.” (HELPinKIDS&Adults 2.0 CPG).³

Evidence: “One study including 150 adults was included in the systematic review whereby vaccines were warmed (either by rubbing or by an incubator) immediately prior to injection (Maiden et al., 2003). There was low level quality of evidence for the outcome of pain (critically important outcome) due to risk of bias and imprecision and no evidence of a benefit of warming the vaccine. Of note, the temperature achieved in the intervention group was below body temperature (by approximately 10 degrees centigrade). Temperatures that are closer to body temperature may be required to have an observable impact on pain, as suggested by a previous systematic review of warming local anaesthetics prior to injection which showed that warming to body temperature effectively reduced infiltration pain (Hogan et al., 2011). It is also important to consider the effect of warming vaccines on their biologic activity. Correct storage and handling of vaccines is of paramount importance to their effectiveness.” (HELPinKIDS&Adults 2.0 CPG Recommendation 15).³

Conclusions

As there no evidence for effectiveness of this intervention and potential for harm if the vaccine is warmed for a duration or to a temperature as to render its components inactive, warming the vaccine was recommended against by the technical consultation group.

5. Vapocoolants

“Vapocoolants are volatile liquids applied on the skin right before the procedure that immediately reduce the temperature of the surface of the skin as they evaporate, resulting in a sensation of cold

at the application site (Hogan, Smart et al., 2014). Vapocoolants may reduce pain by competing with the pain sensation or decreasing the velocity of neural impulse conduction (Hogan, Smart et al., 2014). In some individuals, however, the sensation of cold is itself painful and increases attention on the impending pain of injection. The effectiveness of vapocoolants was examined for 3 different age groups separately (i.e., infants, children, and adults) due to the potential for differences in how the intervention may be perceived across ages.” (HELPinKIDS&Adults 2.0 CPG).³

Vapocoolants: Children up to 3 years

Evidence: “One study was included in the systematic review including 60 infants aged 2 to 6 months of age (Maikler 1991). There was low quality evidence for the outcome of distress (critical outcome) due to risk of bias and imprecision, and no evidence of a benefit.” (HELPinKIDS&Adults 2.0 CPG Recommendation 26).³

Vapocoolants: Age >3-17 years

Evidence: “Five studies including 268 children aged 2 to 12 years were included (Abbott & Fowler-Kerry, 1995; Eland 1981; Cohen et al., 2009; Cohen Reis & Holubkov, 1997; Luthy et al., 2013). Vapocoolants were administered using various techniques (e.g., direct spray, application of a cotton ball sprayed with vapocoolant). There was low quality evidence for pain (critical outcome) due to risk of bias from inconsistent or lack of blinding and imprecision and there was no evidence of a benefit. The results are consistent with the results of a recent systematic review of vapocoolants for venipuncture pain that demonstrated no evidence of a benefit for children up to 18 years (Hogan, Smart et al., 2014). Some children may find application of vapocoolants uncomfortable, which can augment their pain experience. The cold sensation can focus attention on the procedure, further augmenting pain.” (HELPinKIDS&Adults 2.0 CPG Recommendation 27).³

Vapocoolants: Adults

Evidence: “One study including 185 adults was included in the systematic review (Mawhorter, 2004). There was low quality evidence for the outcome of pain (critical outcome) due to risk of bias and imprecision; mixed results were observed for this outcome when measured over different time epochs. For acute pain, the SMD was -0.78 (95% CI -1.08, -0.48). For pain during the recovery phase, the SMD was -0.10 (95% CI -0.39, 0.19).” (HELPinKIDS&Adults 2.0 CPG Recommendation 28).³

Conclusions

Due to the lack of evidence of benefit for this intervention in children, the technical consultation group does not recommend the use of vapocoolants in this population. While vapocoolants may be of benefit in adults they are expensive (about \$1/dose), benefit may be offset by discomfort from application (due to stinging sensation from cold) and the evidence for the effectiveness of other preparations such as topical anaesthetics is more robust.

Appendix 3: Education of clinicians, children, adults and caregivers

Education of Clinicians

Health care providers who routinely give immunizations need to be knowledgeable about evidence based approaches to pain mitigation at the time of immunization as *“individuals receiving vaccinations value efforts made by clinicians to minimize pain and fear as it demonstrates that clinicians are competent and that they care about them (Taddio, Ilersich et al. 2014).”*³ Training of health care providers can support use of evidence based pain mitigation interventions. Caregivers and those receiving vaccine injections can also benefit from education about these strategies.

Evidence: *“One study involving 53 public health nurses delivering vaccinations to 459 children was included in the systematic review (Chan et al., 2013). Public health nurses in the intervention group were trained in a variety of evidence-based pain treatments using a multi-faceted approach: 2-hour in-person education session including a power-point presentation and practice scenarios delivered by a nursing manager, and online support. The control group did not receive this education. There was low quality evidence for critical outcomes (use of pain interventions) due to risk of bias. There was an increase in the use of pain interventions in the training group: SMD 0.66 (95% CI 0.47, 0.85) (N.B. better indicated by higher values).”* (HELPinKIDS&Adults 2.0 CPG Recommendation 45).³

Education caregivers and children

Evidence: *“Five studies were included in the systematic review that evaluated education of 589 parents of children less than 2 years of age prior to the day of vaccination (Bustos et al., 2008; Cramer-Berness 2005 a; Taddio, Parikh et al., 2015; Taddio, MacDonald et al., 2014; Taddio, Smart et al., 2014b). In included studies, parents were trained in a variety of evidence-based pain treatments using different techniques, including: verbal instruction, pamphlets, and videos. Training took place in the hospital during prenatal classes or after delivery of an infant, and at outpatient clinics. These methods are consistent with usual methods and settings of education of the public about immunization. There was moderate to low quality of evidence across different indicators for use of pain interventions (critical outcome) with mixed results. In the analysis that included the largest number of studies (n=300 participants), there was a benefit on use of pain interventions: RR 2.08 (95% CI 1.51, 2.86) (N.B. better indicated by higher values). The results were mixed for distress in the children. In the analysis that included the largest number of studies (n=350 participants), there was a benefit on acute distress: SMD -0.35 (95% CI -0.57, -0.13). There were no data for other critical outcomes (pain, fear) due to the inability of included children to provide self-report as a result of their young age.”* (HELPinKIDS&Adults 2.0 CPG Recommendation 47).³

“Four studies evaluated education of parents of children up to 6 years of age on the day of vaccination (Cohen et al., 2015; Cramer-Berness, 2005a; Taddio, Parikh et al., 2015; Felt et al., 2000). In included studies, parents were trained in clinics using a variety of techniques, including: verbal instruction, pamphlets, computer or videos. There was low to very low quality of evidence due to risk of bias and imprecision for one of the critical outcomes (use of pain interventions) and evidence of a benefit for this outcome. In the analysis including the largest number of participants (n=239), there was a benefit for parent use of intervention: RR 2.42 (95% CI 1.47, 3.99) (N.B. better indicated by higher values). There was a benefit for child use of intervention in one study including 60 children (Cohen et al., 2015): SMD 1.93 (95% CI 1.31, 2.55). There was no evidence of a benefit for pain. The

*results were mixed for measures of child distress. In the analysis including the largest number of children (n=422), there was no evidence of a benefit for acute distress: SMD 0.05 (95% CI -0.89, 0.99). There was no data for the other critical outcome (fear).” (HELPinKIDS&Adults 2.0 CPG Recommendation 48).*³

Education of Individual

*Evidence: “One study involving 51 female children undergoing vaccination aged 11 to 12 years in a school setting was included in the systematic review (Klingman, 1985). Children in the intervention groups were provided with 10 minutes of detailed information about the infectious disease being vaccinated against, the vaccination procedure and cognitive coping techniques. Then they either practiced by imagining the vaccine injection or asked questions. There was very low quality of evidence for the critical outcome of fear due to risk of bias and imprecision. The effects were mixed; there was a benefit for pre-procedural fear [SMD -0.67, 95% CI -1.28, -0.07]] but not acute fear [SMD -0.63 (95% CI -1.62, 0.36)]. There was no data for the critical outcome of pain. In the included study, children were vaccinated in groups of 5 and there may have been some contamination between educated and non-educated groups.” (HELPinKIDS&Adults 2.0 CPG Recommendation 49).*³

Evidence to Decision Elements of GRADE_DECIDE framework:

Benefits and harms: There is moderate to very low evidence for increased use of evidence based pain mitigation strategies with education of healthcare workers and parents and hence benefit. There is no evidence of harm on pain experience. However, teaching people about pain may give them expectation for pain to be treated and just cause for being dissatisfied if not done so adequately. This makes the health care system more accountable for providing quality level of care. As with the HELPinKIDS&Adults 2.0 CPG review team, the WHO review team values the use of these pain and distress mitigation techniques by clinicians *“in order to fulfil their ethical obligation to reduce unnecessary suffering and to demonstrate competency regarding best practices for vaccine injections”*³

Resource use and value for money: For health care providers, the only additional resources required are to build this training into existing education and training programs. For adults, youth, older children and parents opportunistic education could occur at the time of vaccination is discussed such as while waiting to be immunized.

Impacts on equity: There are no anticipated impacts on health inequity.

Acceptability: No concerns were expressed regarding cultural acceptability.

Feasibility (implementability): Education interventions were seen as feasible for those giving vaccines (health care workers), those receiving vaccines (adults, youth, older children) and caregivers. Provision of practical educational resources such as pamphlets, posters, etc., for caregivers, adults and older children and youth could support this process.

Other: None

Appendix 4: Implementation survey participant responses table

Questions: Eight questions related to the categories outlined below- note: “Late” refers to which recommendations participants felt would have a late update and “Early” refers to which recommendations participate felt would have an early update.

Exemplar Recommendations:

1. Do NOT aspirate; 2. Administer vaccines from the least to the most painful; 3. Breastfeed at time of immunizations; 4. Use neutral words at the time of immunization; avoid language that increases anxiety

Country	Culture/gender	Preference/values	Feasibility	Barriers	Acceptability	Late	Early	Cost
Algeria	No issues	Communication, and with MOH support	Without problem	None	Challenge to accept for some	2	3,4	
Botswana	Breastfeeding is culturally encourage	Recs. will be welcome by pts	Yes, but MOH training updates	None	Yes	0	4	Add to EPI-MLM train.
Burkina Faso	For 3, leave the initiative to the mother, if not certain cultural concerns regarding exposing a breast	Knowledge, attitudes, previous experience with vaccines and epi context	Yes, a training with theory and practice with role playing	Noncompliance of workers, the number of vaccines and the service of vaccination, and customs of populations	You need to inform, explain and follow	1,3,4	2	3 days
Cabo Verde	No issues	Nothing	Yes	few barriers	yes	0	1,2,3,4	Some time and reduced costs
Comoros Islands	For some, breast feed not culturally accepted	Good to have regular parent feedback	Training of trainers and cascade training	Poor knowledge of workers	yes	1	2	1/yr train
Cote D'Ivoire	No issues	In general, patient doesn't decide	Yes, with sensitivity training	There are some habits that may need challenging and changing	yes	1	3	Non mentioned

Eritrea	No issues	Preferences for oral vaccines	yes	No aspiration a challenge	Except for Aspiration	1	4	min
Ethiopia	Breast feeding may have culture issues for some	Pts may prefer to start with most painful injection	No aspiration will be challenging	History of neglecting pain, attitudes will need to change	Yes, but need to convince them pain is unacceptable	4,2	1,3	2-3 orientations and link to other training
Ghana	No issues	Lead to higher patronage for vaccination	Very feasible	No barriers anticipated	Yes	0	1,2,3,4,	2 months for a cascade of training from national to district levels
Liberia	No issues	Increased acceptance which lead to good coverage	Very feasible	Most workers still use words that will anger the caregiver	Yes	3	1	Request proper planning/budgeting based on needs
Madagascar	No issues	Pain has importance to parents to 2,4 are important	Need formative supervision along with training	Workers need additional training- and to communicate	Yes, if trained	4	2	Include in training, monitor, beyond HSS needed
Malawi	No issues	None	Easy to do	# of injections could be a challenge	Yes	4	1,2,3	No extra cost, link to current content and HCW training
Mali	Yes	Experience of Uniject led to rumours of risk of sterilization/contraception	Yes	Minimum barriers	Yes	0	1	Training of 3 or 4 days will be necessary and into the training cascade
Mauritania	No issues	No concerns	Yes feasible	#3 not easy to implement because the mothers are not always available during vaccination	Yes	1,4	1,2	Yes +++ training of workers, and agents of vaccination

Mauritius	No issues	There will be no impact	It's not worth training	If you don't aspirate you might give vaccine in blood vessel	No	none	none	Number 4 only one worth training
Mozambique	No issues	Good acceptability	Integrate for new vaccines this year	Worried mothers need to hold baby for vaccine so breastfeeding would interfere	Yes but with scepticism because aspiration contradict previous training	1,3	2,4	Cost bearable if integrate to new vaccine, but substantial if done alone
Namibia	No issues	Does not think patient preference have impact	Training of workers is continuous and dynamic	Explanation of reasons will reduce barriers	Yes	0	all	Needs time for sure, these recommendations are not too many to need a lot of time
Niger	No issues	No impact	Yes, why not	In principle, but not without getting used to and encouragement	Yes, but it will demand some time	3	1,2,4	Cost of adapting
R. Guinea	No issues	No elements	Yes	Need training, need directives for the new ones, need supervision	Yes	3	1,2,4	Little info on breastfeeding, little costs
Sierra Leone	No issues	Acceptance	Very feasible, communication must be emphasized	Barriers: order of injection from least to most painful may not be adhered to without proper	Yes, with appropriate training- especially communication	1	3	Moderate to high

				training				
Swaziland	None in Swaziland	No impact	Very feasible	Health worker fear inflicting pain with multiple injections	Yes they will accept them	none	all	Not much cost as these can be communicate in various forums and posters etc..
Tanzania	No issues or very minimal		Feasible if linked to new vaccine	Sometimes workers mirror the child pain when cry with them, but generally are positive	Yes	4	1	
Uganda	No issues	Parents more concerned about pain reaction after and want meds to help with this	No aspiration could be confusing given policy for adrenal injection	Yes, as long as evidence is provided	Yes with evidence	1	3	Minimal
Zambia	No issues identified	3 is more or less a Recommendation in Zambia, number 4 may have some impact	A separate training not feasible, best to align with introduction of new vaccine	Changing from traditional aspiration, and neutral words, and putting each child on a feed all potential barriers	Yes but it will take time	1	3	Separate training not feasible, link to other training, difficult to attach cost
Zimbabwe	No issues	With good program communication no problems anticipated	Quite feasible	Giving too many injects, workers don't like inflicting too much pain	Yes	none	Most in practice	Integrate into ongoing trainings an supportive supervision and may not incur any separate costs

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