Author(s): VS/AT **Date:** 2015-03-26

Question: Should sucrose solution vs placebo/no treatment be used for reducing vaccine injection pain in children up to 2 years?^{1,2}

Settings: hospital, clinics

Bibliography: Allen 1996 (1-12), Barr 1995, Chattopadhyay 2011, Dilli 2009 (3), Harrison 2014 (1,2), Hatfield 2008, Hatfield 2008 a, Harrington 2012 (3,4), Lewindon 1998, Liaw 2011 (2), Moradi 2012 (1,2), Mowery 2008, Poulsen 2009, Priambodo 2008, Ramenghi 2002 (1,2), Sahebihagh 2011 (4), Soriano Faura 2003, Yilmaz 2014 (1,2)

Quality assessment							No of patients		Effect		Importance
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sucrose solution	Placebo/no treatment	Relative (95% CI)	Absolute		
Scale 0-10, Ur	niversity o	of Wisconsin Chi									
	no serious risk of bias	no serious inconsistency ⁷	no serious indirectness	no serious imprecision	none	421	460	-	SMD 0.37 lower (0.67 to 0.06 lower) ^{3,4,5}	⊕⊕⊕⊕ HIGH	CRITICAL
						0-7, Modifi	ed Riley Pain	Score 0-9,	Faces Legs Activi	ty Cry Cons	olability 0-10
	no serious risk of bias	no serious inconsistency ⁷	no serious indirectness	no serious imprecision	none	1134	937	-	SMD 0.76 lower (1.19 to 0.34 lower) ^{4,5,8,9,10}	⊕⊕⊕⊕ HIGH	CRITICAL
										Pain Scale 0	-10,
_	no serious risk of bias	no serious inconsistency ⁷	no serious indirectness	no serious imprecision	none	308	359	-	SMD 0.5 lower (0.96 to 0.03 lower) ^{3,4,5}	⊕⊕⊕⊕ HIGH	CRITICAL
	Acute ^{3,4,5} (mescale 0-10, Urs; Better indivariant in	Design bias Acute ^{3,4,5} (measured we cale 0-10, University of special properties of bias Acute + Recovery ^{4,5,8,9} randomised no serious risk of bias Acute + Recovery ^{4,5,8,9} randomised no serious risk of bias Recovery ^{3,4,5} (measure by of Winsconsin Childer randomised no serious risk of bias	Design Risk of bias Inconsistency Acute ^{3,4,5} (measured with: validated too cale 0-10, University of Wisconsin Chis; Better indicated by lower values) randomised trials ⁶ no serious risk of bias no serious inconsistency ⁷ Acute + Recovery ^{4,5,8,3,10} (measured with tion) by researchers, parents and clinic randomised trials ¹¹ no serious risk of bias no serious risk of bias no serious risk of bias no serious inconsistency ⁷ Recovery ^{3,4,5} (measured with: validated by of Winsconsin Children's Hospital Parandomised randomised	Design Risk of bias Inconsistency Indirectness Acute ^{3,4,5} (measured with: validated tools (Neonatal I icale 0-10, University of Wisconsin Children's Hospits; Better indicated by lower values) randomised trials ⁶ no serious inconsistency ⁷ no serious indirectness Acute + Recovery ^{4,5,8,9,10} (measured with: validated tools) Acute + Recovery ^{4,5,8,9,10} (measured with: validated tools) randomised no no serious inconsistency ⁷ no serious indirectness randomised trials ¹¹ no serious inconsistency ⁷ no serious indirectness Recovery ^{3,4,5} (measured with: validated tools (Neona by of Winsconsin Children's Hospital Pain Scale 0-20) randomised no serious inconsistency ⁷ no serious indirectness inconsistency ⁷ no serious indirectness inconsistency ⁷ indirectness	Design Risk of bias Inconsistency Indirectness Imprecision Acute ^{3,4,5} (measured with: validated tools (Neonatal Infant Pain Scale 0-10, University of Wisconsin Children's Hospital Pain Scale 0 serious risk of bias Inconsistency Inconsistency Inconsistency Indirectness Imprecision Acute + Recovery 4,5,8,9,10 (measured with: validated tools (Neonatal Infant Pain serious risk of bias Inconsistency Incons	Design Risk of bias Inconsistency Indirectness Imprecision Considerations Acute ^{3,4,5} (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Ficale 0-10, University of Wisconsin Children's Hospital Pain Scale 0-20, Faces Legs As; Better indicated by lower values) Trandomised trials no serious inconsistency indirectness	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Solution Acute ^{3,4,5} (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Codit (Scale 0-10, University of Wisconsin Children's Hospital Pain Scale 0-20, Faces Legs Activity Crysts; Better indicated by lower values) Trandomised no no serious inconsistency risk of bias no serious indirectness imprecision none with trials not risk of bias no serious indirectness imprecision none risk of bias no serious inconsistency no serious indirectness imprecision none serious inconsistency no serious indirectness imprecision none serious inconsistency no serious indirectness imprecision none serious ser	Design Risk of bias Inconsistency Indirectness Imprecision Considerations Solution Interaction Real Placebo/no treatment Acute ^{3,4,5} (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Coding System 0-4 (Scale 0-10, University of Wisconsin Children's Hospital Pain Scale 0-20, Faces Legs Activity Cry Consolability (Strick of bias) Trials no serious inconsistency indirectness imprecision none 421 460 Acute + Recovery 4,5,8,3,10 (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Modified Riley Pain tion) by researchers, parents and clinician; Better indicated by lower values) Trandomised no no serious inconsistency indirectness indirectness imprecision none 1134 937 Recovery 1,5,6,6 (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Coding System by of Winsconsin Children's Hospital Pain Scale 0-20) by researchers, parents and clinicians; Better indicated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Coding System by of Winsconsin Children's Hospital Pain Scale 0-20) by researchers, parents and clinicians; Better indicated to serious inconsistency indirectness	Design Risk of bias Inconsistency Indirectness Imprecision Considerations Solution treatment (95% CI) Acute ^{3,4,5} (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Coding System 0-48, Modified Cale 0-10, University of Wisconsin Children's Hospital Pain Scale 0-20, Faces Legs Activity Cry Consolability 0-10, Cry s; Better indicated by lower values) Fandomised no serious inconsistency indirectness i	Design Risk of bias Inconsistency Indirectness Imprecision Considerations Solution Considerations Color Considerations Color Color Considerations Color Considerations Color Color Consideration Color Color Considerations Color Co	Design Risk of bias Inconsistency Indirectness Imprecision Considerations Solution Place (95% CI) Absolute Acute 3-4.5 (measured with: validated tools (Neonatal Infant Pain Scale 0-7, Neonatal Facial Coding System 0-48, Modified Behavioural Pain Scale 0-10, University of Wisconsin Children's Hospital Pain Scale 0-20, Faces Legs Activity Cry Consolability 0-10, Cry duration) by researchers, pare species in indicated by lower values) randomised no serious inconsistency indirectness imprecision in one within trials one serious inconsistency indirectness in precision in oserious serious inconsistency indirectness in precision in oserious indirectness in precision in oserious serious inconsistency indirectness in precision in oserious indirectness in precision indirectness in precision in oserious indirectness in precision indirectness indirectnes indirectness indirectness indirectness indirectness indirectness indirectness in

	randomised rials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹²	none	127/371 (34.2%)	159/186 (85.5%)	RR 0.37 (0.2 to 0.69) ¹⁰	539 fewer per 1000 (from 265 fewer to 684 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-	-	
istress /	Acute + Rec	overy (ye:	s/no) (assessed	with: validated	tools (Neonata	al Infant Pain Sca	le 0-7, cryi	ng) by researc	cher)		ļ.	
lr												
	randomised rrials ¹¹	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹³	none	26/87 (29.9%)	45/88 (51.1%)	RR 0.71 (0.27 to 1.87)	148 fewer per 1000 (from 373 fewer to 445 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-	-	
afety (as	ssessed with	observa	lation of infant fo	r cough or gag	aina)			0%		<u>-</u>		
		0.000. 1			gg/							
	randomised rials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹⁴	none	4/119 (3.4%)	1/117 (0.85%)	RR 2.83 (0.45 to 17.61) ¹⁵	16 more per 1000 (from 5 fewer to 142 more)		IMPORTAN'
								0%		-	1	
rocedur	e Duration (measured	with: validated	tool (stopwatch	h, number of se	econds) by resea	rcher; Bett	er indicated b	y lower va	lues)		
		T	· ·	1 .	. 13	1	0.5	0.4		0145 0 45 1		IN ADODTANI
	randomised rrials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹³	none	25	24	-	SMD 0.15 lower (0.71 lower to 0.41 higher)	⊕⊕⊕O MODERATE	IMPORTAN'
se of Int	ervention ¹⁶	(assessed	d with: acceptab	ility/acceptance	e by infant)							
	randomised rials	no serious	no serious inconsistency	no serious indirectness	serious ¹²	none	-	-	not pooled ¹⁶	not pooled ¹⁶	⊕⊕⊕O MODERATE	IMPORTAN
		risk of bias						0%		not pooled		
arent Pr	eference ¹⁷ (a	assessed	with: questionn	aire about futu	re use)							
	randomised rials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision ¹⁴	none	-	-	-	-	⊕⊕⊕⊕ HIGH	IMPORTAN
		risk of bias						0%		-		
		1			I	1						

Parent F	Parent Fear, Vaccine Compliance, Preference, Satisfaction (assessed with: no data were identified for these important outcomes)												
0	No evidence available					none	-	-	-	-		IMPORTANT	
								0%		-			

In included studies, the concentration of sucrose solution ranged from 12% to 75%; the dose was not specified in one study, however, it was described as a saturated solution. The volume used was 2 mL in all but 3 studies where it was 0.75 mL (Barr 1995) and 0.6 mL/kg (Hatfield 2008, 2008a).

² In the studies by Allen (7-12), Dilli 2009 (3), Liaw 2011 (2), and Sahebihagh 2011 (4), there was a no treatment control group; the remaining studies included placebo water.

³ In study by Poulsen (2009), data are not provided; however, researchers report no statistically significant differences between groups. That study compared 12% sucrose to placebo water.

⁴ In the study by Moradi (2012), the sample size in the control group was divided by 2.

⁵ In the study by Allen 1996, the sample size in the sucrose group was divided by 2

⁶ Study by Poulsen (2009) could not be included in the meta-analysis as pain scores not provided for intervention (sucrose) and control (water) group

⁷ Heterogeneity can be explained by variability in dose, administration technique and personnel involved, cointerventions, and age of participants

⁸ In the study by Harrington (2012), oral rotavirus vaccine was administered prior to vaccine injections; since this vaccine contains sweet-tasting substances, there may have been contamination

⁹ In the study by Ramenghi 2002, the sample size in the control group was divided by 2.

¹⁰ In the study by Yilmaz (2014), the sample size in the control group was divided by 2.

¹¹ In study by Chattopadhya (2011), the concentration of sucrose solution is not specified; however, it is reported to be a saturated solution

¹² Sample size was below the recommended optimum information size (OIS) of 400 for an effect size of 0.2

¹³ Confidence interval crosses line of nonsignificance and sample size was below the recommended optimum information size (OIS) of 400 for an effect size of 0.2

¹⁴ Sample size was below the recommended optimum information size (OIS) of 400 for an effect size of 0.2

¹⁵ Duration < 10 seconds and not clinically important

¹⁶ In 1 study (Hatfield 2008), 4/100 (4%) of infants refused to accept sucrose. Separately, in study of tactile stimulation vs control whereby all infants were given sucrose (Taddio 2014 a), 28/121 (23%) were unsettled or crying during sucrose administration.

¹⁷ In study by Harrison 2014 (1.2), only 2 parents reported they would not use the intervention (sucrose or water) out of 29