

Differences in Immunization Site Pain in Toddlers Vaccinated with Either the 10- or the 13-Valent Pneumococcal Conjugate Vaccine

Johannes Trück, MD, DPhil,^{1,2*} Sarah Kelly, MSc,¹ Sena Jawad, MSc,³ Matthew D. Snape, FRCPCH,¹ Merryn Voysey, M.Biostat,³ and Andrew J. Pollard, FRCPCH, PhD¹

¹Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, UK

²Division of Immunology and the Children's Research Center, University Children's Hospital, University of Zurich, Zurich, Switzerland

³Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

***Corresponding author:** Johannes Trück MD, DPhil, Division of Immunology and the Children's Research Center, University Children's Hospital, University of Zurich, Zurich, Switzerland; tel.: +41 44 266 7111; fax: +41 44 266 7311. E-mail: johannes.trueck@kispi.uzh.ch

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Conflicts of interest AJP has previously conducted studies on behalf of Oxford University funded by vaccine manufacturers, including the present study, but currently does not undertake industry funded clinical trials. AJP chairs the UK Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI); the views expressed in this manuscript do not necessarily reflect the views of JCVI or DH. M.D.S. acts as chief or principal investigators for clinical trials conducted by the University of Oxford, sponsored by vaccine manufacturers, but receives no personal payments from them. M.D.S. has participated in advisory boards and industry sponsored symposia for vaccine manufacturers, but receives no personal payments for this work. M.D.S. and J.T. have received financial assistance from vaccine manufacturers to attend scientific conferences. The other authors have no conflicts of interest to disclose.

Abstract

We investigated immediate immunization pain in 12-month-old children randomized to receive a booster dose of either the 10- (PCV-10) or the 13-valent (PCV-13) pneumococcal conjugate vaccine. Pain was assessed using validated pain assessment tools and crying time. PCV-13 recipients had significantly higher scores on the observer-rated modified behavioral pain scale than did those receiving PCV-10, but the differences were small.

(60 words)

Clinical trial registration at [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT01443416)

Key words: adverse event; acute pain; immunization site pain; pneumococcal conjugate vaccine; children

Introduction

Immunization site pain represents one of the most common complaints following vaccine administration [1]. It is an unpleasant experience for both children and their parents and may contribute to needle phobia, anxiety and distress associated with a health care provider's appointment and may ultimately result in non-adherence to vaccination schedules [2,3].

Although several previous vaccine trials have included immunization site pain as an adverse event following vaccination, different methods of assessment have been used. In 2012, the Brighton Collaboration published standardized criteria for the evaluation and reporting of immunization site pain allowing for comparability and uniform reporting of pain across different studies [4]. Their recommendations include assessment tools for the evaluation of immediate pain following vaccination and, to the best of our knowledge, this is the first clinical vaccine trial in children using the approach suggested in this guideline. Very few studies have investigated the intensity of immediate pain and distress at the time of vaccine injection by evaluating different brands of vaccines. Immediate pain refers to the sensation of pain in response to vaccine administration at the vaccination site [4]. Differences in immediate pain at vaccination have been observed for different brands of the MMR vaccine in 4 RCTs [5–8] resulting in the suggestion of several national guidelines to use the least painful vaccine if more than one product is available and the products are interchangeable [9,10].

There are 2 pneumococcal conjugate vaccines that are currently in use in national immunization schedules, i.e. those containing 10 and 13 pneumococcal serotypes (PCV-10 and PCV-13), respectively. Both vaccines have been shown to effectively protect against invasive pneumococcal disease when several doses are given to young children. Here, we report the investigation of immediate pain following booster vaccination of 12-month-old children with

either PCV-10 or PCV-13 in a randomized vaccine trial. Pain during vaccine administration was studied using validated pain assessment tools and crying time to investigate factors that may interfere with parental compliance to vaccination. Targeting these factors in future vaccine trials with the aim of reducing immediate injection site pain might help decrease vaccine hesitancy and hence improve immunization coverage.

Methods

Immediate injection site pain was assessed as a secondary objective in a randomized vaccine trial involving healthy 12-month-old children (n=178) [11,12]. Ethical approval was obtained from the Oxfordshire Research Ethics Committee (11/SC/0473) and the study was registered on Clinicaltrials.gov (NCT01443416). Children were randomized to receive a booster dose of either the 10-valent pneumococcal conjugate vaccine (PCV-10, Synflorix®, GSK Biologicals) or PCV-13 (Prevenar 13®, Pfizer) following PCV-13 immunization at 2 and 4 months of age. The primary objective of the study was the assessment and comparison of the immunogenicity of the different vaccines, the results of which have been reported previously [11,12].

Blood samples were taken immediately prior to vaccination at 12 months of age, after which immediate pain at time of injection was determined using validated pain assessment tools and crying time [4,13,14]. As children aged 12 months are unable to articulate the degree of pain they experience, pain measurement was conducted on behalf of the children as suggested by the Brighton Collaboration [4]. As much time as possible (usually between 5 to 10 min) was allowed following drawing blood for the child to settle before the booster vaccine was given. As a possible confounding factor, “baseline mood” (with the reported dimensions “calm”, “crying” or “distressed”) was recorded at the time of vaccination. Both vaccines were administered intramuscularly using a 0.6 x 25 mm 23-gauge needle into the anterolateral aspect of either thigh.

The child was sat in the parent's lap and held securely by the parent by means of wrapping one of the child's arms around the parent's waist and the parent holding the child's other arms across the body and holding the legs. Vaccines were administered at room temperature.

The Modified Behavioral Pain Scale (MBPS, 0-10) was used to determine pain and was completed by a second member of the study team who did not administer the vaccine and was blinded to which vaccine was injected. The pain score assessors were specifically trained with an internal SOP using different videos showing children experiencing pain. Parents were asked to use the Numerical Rating Scale (NRS, 0-10) to estimate the pain intensity of their children. Finally, the duration of crying from the moment of needle insertion until all crying activity had ceased was recorded by study staff. Pain assessments were recorded on the diary card (Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/C927>).

Pain was compared between vaccine groups using an analysis of covariance (ANCOVA) adjusting for sex, age, ethnicity, baseline behavior, site of injection, vaccinator and the observer for MBPS (Table 1).

Results

A total of 178 study participants were enrolled into the study, of which 87 and 90 received PCV-10 and PCV-13, respectively; one study participant withdrew consent before vaccination [11]. As there were several teams involved in the study, pain scores were randomly assessed by a total of 6 different people (Fig., Supplemental Digital Content 2, <http://links.lww.com/INF/C928>) and, if a second person was not available, were not evaluated at all resulting in around 14% missing data, which were equally distributed between the groups (Table 1). The difference in pain scores between the PCV-13 and PCV-10 groups did not vary between assessors.

Pain assessed by the MBPS was measured with a median score of 7 (IQR 6–8) in the PCV-10 group and 8 (IQR 7–9) in the PCV-13 group (Table 1 and Fig. 1). None of the children in either group scored less than 3 and there were 29 (39%) and 46 (58%) study participants with scores of 8 or more following booster vaccination with PCV-10 and PCV-13, respectively (Table 1 and Fig., Supplemental Digital Content 3, <http://links.lww.com/INF/C929>). MBPS scores in PCV-10 recipients were significantly lower than in PCV-13 recipients although the overall difference between groups was only modest (adjusted group difference: 0.72 points in the MBPS, 95% CI 0.29–1.15, $p=0.001$) (Table 1 and Fig. 2).

For the NRS assessed by a parent, median scores were 5 (IQR 4–7) and 6 (IQR 4–7) in the PCV-10 and PCV-13 group, respectively (Table 1 and Fig. 2). The distribution of scores was similar in both groups and only few participants ($n=9$ in each group) were given scores of 8 and higher (Table 1 and Fig., Supplemental Digital Content 3, <http://links.lww.com/INF/C929>). There was no statistically significant difference between the groups for the NRS (adjusted group difference 0.532, 95% CI -0.13–1.19, $p=0.114$) (Table 1).

The duration of crying following vaccination ranged from 0 to 152 seconds with no statistically significant differences between the 2 groups (Table 1 and Fig. 1). When adjusted for sex, age, ethnicity, baseline behavior, site of injection, and vaccinator, the overall crying time was no different in the PCV-13 compared with the PCV-10 group (adjusted group difference 4.3 seconds, 95% CI -4.8–13.4, $p=0.35$). However, the duration of crying across both groups was significantly lower when the child's behavior before vaccination was judged by the observer as “calm” compared with “crying” (mean duration of crying for both groups: 35.5s vs. 55.1s; $p=0.011$, data not shown). MBPS scores were also significantly higher in “crying” children compared with “calm” children (mean MBPS 8.5 vs. 7.2; $p<0.001$, data not shown). No effect of

baseline mood on parent-derived NRS was found (Fig., Supplemental Digital Content 4, <http://links.lww.com/INF/C930>).

Discussion

By using validated assessment tools suggested by the Brighton Collaboration [4], we show that PCV-10 administration is associated with slightly less acute pain compared with the injection of PCV-13. This was demonstrated by significantly lower MBPS scores in PCV-10 compared with PCV-13 recipients.

In general, mean MBPS scores were high for both vaccines. A previous study similarly used MBPS for pain assessment in a vaccine trial involving 2-6 months old children who were given pentavalent routine vaccine (DTaP-Hib; Pentacel, Sanofi Pasteur) and 7-valent pneumococcal conjugate vaccine (PCV-7; Prevnar, Wyeth) [15,16]. In that study, receipt of PCV-7 was associated with significantly higher pain scores than DTaP-Hib (means 8.2 vs. 6.3) suggesting that PCV-7 (the predecessor of PCV-13 and produced in a similar manner) is a more painful vaccine than other routine vaccines such as the DTaP-Hib vaccine.

There are limited data comparing immediate pain between different brands of similar vaccines and one can only speculate on the mechanisms that underlie pain responses at vaccine injection. The difference in pH of the injected material has previously been suggested as a possible explanation for the observed variation in pain using two measles-mumps-rubella vaccines [7,14]. PCV-13 is slightly acidic than PCV-10 (5.8 vs. 6.1) but other differences in the contents and physico-chemical properties of the two vaccines (Table, Supplemental Digital Content 5, <http://links.lww.com/INF/C931>) may also affect the pain response. Needle size has previously been shown to affect reactogenicity following infant immunization [17] but whether it also affects pain responses during vaccine injection is unknown and may be a topic for further study.

As a limitation of the study, pain scores were assessed by several operators. Although the assessors were blinded to the vaccine given, videotaping the pain reaction and scoring afterwards may be an alternative and possibly a more standardized approach. Pain scores were affected by the “mood” of the child following the blood draw and before vaccination. However, results are reported after adjusting for known confounders and given the design of the study, possible unknown confounders are likely distributed equally across the 2 groups.

In summary, we found that injection with PCV-13 induced significantly more pain than injection with PCV-10 when assessed with a validated observed-rated pain tool, however the size of the difference was small and is of unknown clinical significance. The number of vaccines that are recommended for infants has been increasing over the past 20 years. Factors that are associated with pain and distress following vaccination may interfere with parental compliance and add to the current upsurge of vaccine hesitancy. Therefore, evaluating and minimising the factors that are associated with vaccination pain might improve tolerability of vaccines and hence vaccine acceptance.

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Figure legends

Fig. 1 Boxplots of pain assessment scores and crying time by vaccine group. P-values are taken from ANCOVA. The median is shown as a line across the box (with the median value written above the line) and the box represents the lower and upper quartiles. Whiskers extend to the maximum or minimum values within 1.5 times the IQR above and below the 3rd and 1st quartile, respectively. Points outside this range are represented as dots.

SDC 1. Excerpt of the diary card showing how pain assessment tools were used and recorded in the study [figure]

SDC 2. Boxplots of MBPS pain score and crying time by observer. Numbers above the boxplots indicate the sample size per group and observer [figure]

SDC 3. Histograms of number of observations by pain score and vaccine group [figure]

SDC 4. Boxplots of pain scores and crying time by the mood of children before vaccination and study group. Numbers above the boxplots indicate the sample size per group and mood [figure]

SDC 5. Physico-chemical properties of pneumococcal conjugate vaccines [table]

Table 1 Summary table for immediate pain at time of immunisation by vaccine group

	PCV-13		PCV-10		ANCOVA Adjusted Group Effect*	95% Confidence Interval	P-Value
	N	(%)	N	(%)			
Modified Behavioural Pain Scale (MBPS)					0.722	0.292, 1.153	0.001
0	0	(0)	0	(0)			
1	0	(0)	0	(0)			
2	0	(0)	0	(0)			
3	1	(1.1)	2	(2.3)			
4	2	(2.2)	1	(1.1)			
5	1	(1.1)	4	(4.6)			
6	11	(12.2)	15	(17.1)			
7	18	(20.0)	23	(26.1)			
8	21	(23.3)	15	(17.1)			
9	17	(18.9)	8	(9.1)			
10	8	(8.9)	6	(6.8)			
Total	79	(87.8)	74	(84.1)			
Missing	11	(12.2)	14	(15.9)			
Median (IQR)	8 (7-9)		7 (6-8)				
Mean (SD)	7.7 (1.5)		7.2 (1.5)				
Numerical Rating Scale (NRS)					0.532	-0.129, 1.19	0.114
0	0	(0)	0	(0)			
1	0	(0)	3	(3.4)			
2	4	(4.4)	5	(5.7)			
3	9	(10.0)	9	(10.3)			
4	9	(10.0)	9	(10.3)			
5	12	(13.3)	13	(14.9)			
6	14	(15.6)	12	(13.8)			
7	23	(25.6)	17	(19.5)			
8	7	(7.8)	8	(9.2)			
9	2	(2.2)	0	0			
10	0	0	1	(1.1)			
Total	80	(88.9)	77	(87.5)			
Missing	10	(11.1)	11	(12.5)			
Median (IQR)	6 (4-7)		5 (4-7)				
Mean (SD)	5.6 (1.8)		5.3 (2.0)				
Crying Time (Seconds)					4.31	-4.79, 13.42	0.350

	PCV-13		PCV-10		ANCOVA	95% Confidence	P-Value
	N	(%)	N	(%)	Adjusted Group Effect*	Interval	
N (Mean) {SD}	78	(41.0)	74	(36.4)	{21.5}		
[Min-Max]		{29.2}		[0-97]			
		[0-152]					

*Adjusted for sex, age, ethnicity, baseline behaviour, site of injection, vaccinator (and observer for MBPS only)

IQR, interquartile range; N, number of observations; SD, standard deviation

ACCEPTED

Figure 1

