Optimal technique for intramuscular injection of infants and toddlers: a randomised trial

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ABSTRACT

Objective: To compare the rates of adverse reactions and parental approval ratings for three different techniques for anterolateral thigh vaccination in children aged 2, 4, 6 and 18 months.

Design: Randomised, observer-blind trial.

Participants: 375 children who received pertussis-containing vaccines in a regional New South Wales town between 29 May 2001 and 30 June 2002.

Interventions: Children were randomised to receive intramuscular injection with acellular pertussis-containing and *Haemophilus influenzae* type b vaccines with one of three recognised injection techniques (Australian, World Health Organization or United States).

Main outcome measures: Local adverse reactions (bruising and redness/swelling), systemic adverse reactions (irritability, perceived fever, persistent crying/screaming, drowsiness, vomiting/poor feeding) and parental acceptance were assessed 24 hours after injection.

Results: 361 children (96%) were evaluated 24 hours after vaccination. The WHO technique resulted in significantly fewer children, than with the other two techniques, with the systemic adverse reaction variable "irritability" ($P = 0.0039$). There was a significant difference between the technique groups overall for the local adverse reaction "bruising" with acellular pertussis-containing vaccines ($P = 0.0418$), due to a lower reaction rate in the WHO group compared with the US group ($P = 0.0356$).

Conclusion: The WHO technique appears to be the optimal technique for anterolateral thigh injection in children — it ensures that the injection is intramuscular, results in fewer adverse reactions, and is the easiest technique to perform as it does not require angling of the needle to the long axis of the femur.

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Optimal paediatric vaccination practice (injection site, injection technique and needle gauge and length) has not been rigorously defined.

After the use of adjuvanted diphtheria, tetanus and pertussis vaccines was established in the 1940s, one of the pioneers in this area published a detailed outline of a vaccination practice that minimised severe local adverse effects.[1] This involved deep injection into the lateral gluteal muscle mass with a 25 gauge, 1/2 inch or 5/8 inch needle, terminating each dose with 0.1 mL of air, the latter to prevent vaccine draining back along the injection tract into the subcutaneous tissue. Subsequently, vaccination techniques have been modified in response to reports of vaccination experience in the medical literature.

The gluteal site of injection was abandoned in favour of the anterolateral thigh because of the risk of sciatic nerve injury with viscous agents like penicillin.[2] However, vaccine-induced sciatic nerve injury has never been reported, despite international canvassing for cases by MacDonald and Marcuse.[3]

Angling of the needle to the long axis of the thigh at muscle entry, as in techniques recommended by United States[4] and Australian[5] vaccine advisory groups, is related to a report by Talbert et al of gangrene of the foot in an infant after intramuscular injection of penicillin, with the needle entering the thigh muscle at 90° to the long axis of the femur.[6] No neurovascular adverse reactions have been reported after vaccination with needle entry at this angle in the thigh.

The recommendation for the use of 23 gauge, 25 mm long needles for anterolateral thigh intramuscular injection derives from a study by Hick et al, who measured subcutaneous layer thickness in 4-month-old infants, concluding that a 16 mm long needle introduced at an angle of 45° would penetrate muscle in only 5/24 subjects (21%).[7] Unfortunately, the results of this very small study have not been reproduced. Two other similar studies in 40[8] and 58[9] infants indicated that intramuscular injection would be routinely achieved using a 16 mm long needle and the technique advocated by the World Health Organization.[10]

Clinical trial support for the use of the 23 gauge, 25 mm long needles has been drawn from a small study by Diggle and Deeks[11] that had significant methodological weaknesses.

There are three techniques currently recognised for anterolateral thigh vaccination: the Australian, WHO and US techniques. We conducted a single centre, randomised, observer-blind clinical trial to compare the reactogenicity and parental approval for these three techniques. We used acellular pertussis-containing and *Haemophilus influenzae* type b vaccines in accordance with the Australian Standard Vaccination Schedule.

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METHODS

Vaccination

Vaccinations were given according to the Australian Childhood Immunisation Schedule[5] with diphtheria–tetanus–acellular pertussis–hepatitis B vaccine (InfanrixHepB, [GlaxoSmithKline]) (children aged 2, 4 and 6 months) and diphtheria–tetanus–acellular pertussis vaccine (Infanrix, [GlaxoSmithKline]) (children aged 18 months). *Haemophilus influenzae* type b conjugate vaccine (Pedvax, [Merck Sharp & Dohme]) was given concurrently with the same technique as the acellular pertussis vaccine into the contralateral thigh of children aged 2 and 4 months. Oral polio (Sabin) vaccine (two drops) was given to children aged 2, 4 and 6 months.

Vaccination technique

The three intramuscular injection techniques used were:

Australian — the needle was inserted at the junction of the upper and middle thirds of the vastus lateralis with the needle angled at 45°–60° to the skin and pointing down towards the knee.[5]

World Health Organization — the needle was inserted into the anterolateral thigh at an angle of 90° to the long axis of the femur with the skin compressed between the index finger and the thumb.[10]

United States — the needle was inserted into the upper lateral quadrant of the thigh at an angle of 45° to the long axis of the femur and posteriorly at an angle of 45° to the table top, with the baby supine. The thigh muscle was bunched at the injection site to increase muscle mass and to minimise the chance of striking bone.[4]

Needle gauge and length

The injections using the Australian and US techniques were made with 23 gauge, 25 mm long needles, and the WHO technique injections were made with a 25 gauge, 16 mm long needle.

The shorter needle was used with the WHO technique, as previous studies have shown that a 25 mm long needle would make bony contact if fully inserted.[8,9]

Participants

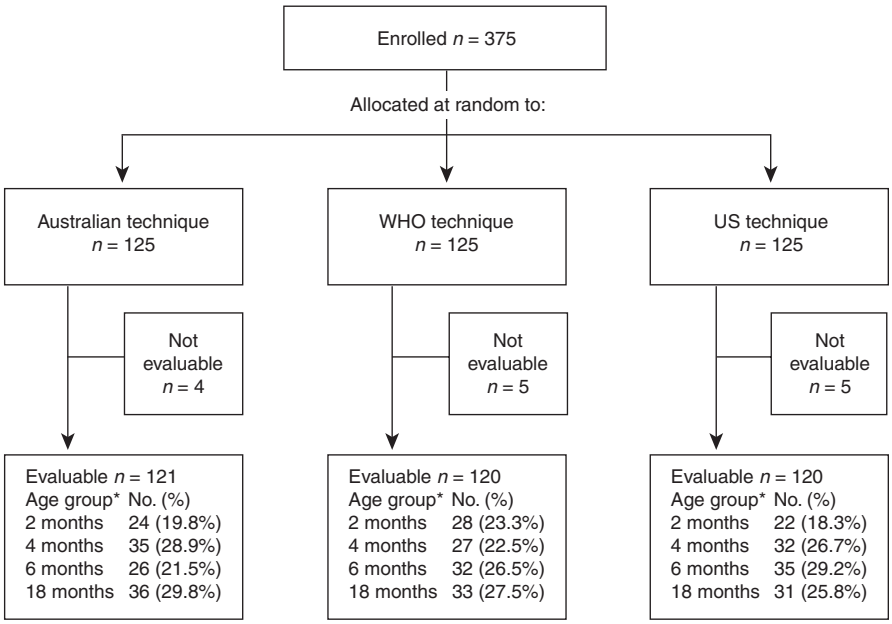
Children aged 2, 4, 6 and 18 months attending a solo practice in Taree, New South Wales, from 29 May 2001 to 30 June 2002, were included in the study if:

- they were in apparent good health at the time of vaccination; and
- written informed consent was obtained from the child's parent(s)/guardian.

Study design

This was a single centre, randomised, observer-blind trial. Randomisation to the three techniques was on a 1 : 1 : 1 basis using computer-generated random numbers. At recruitment, the practice nurse recorded the child's details and arranged a follow-up vaccination review appointment at the practice the next day. She gave the vaccinator (I F C) a sealed envelope containing the random number. The vaccinator prepared the vaccines accordingly, and placed them in a covered kidney dish. The vaccinees were injected with the vaccinator's body obscuring as much as possible the parents' view of the procedure and without being seen by the practice nurse. The child's details (age, technique) were recorded in a manifesto available only to the vaccinator.

1 Profile for clinical trial of three vaccination techniques (Australian, World Health Organization and United States)



* Age ranges were as follows: 2 months, range 8–10 weeks; 4 months, range 15–18 weeks; 6 months, range 23–28 weeks; 18 months, range 68–78 weeks. ◆

Postinjection assessment

The study outcome measures — local adverse reactions (bruising and redness/swelling), systemic adverse reactions (irritability, perceived fever, persistent crying/screaming, drowsiness, vomiting/poor feeding) and parental acceptance — were assessed 24 hours after injection by the practice nurse, as in other pertussis vaccine reactogenicity studies.[12,13]

A previously validated research instrument[14] was used to objectively assess local reactions — bruising and redness/swelling — on a visual analogue scale (VAS), where 0 = no reaction and 5 = whole leg involved; and subjectively (parent) reported irritability, perceived fever, persistent crying/screaming, drowsiness, vomiting/poor feeding on a VAS, where 0 = no reaction and 5 = very severe reaction. Likewise, parental rating of vaccination outcome was scored 0 = very happy and 5 = very unhappy.

Ethical approval

Our study was approved by the Monash University Standing Committee on Ethics in Research using Humans.

Statistical analysis

The sample size was based on the anticipated proportion of patients with redness/swelling after vaccination. It was expected that 37.6% of patients would experience redness/swelling with the WHO technique,[14] compared with 20% with each of the US and Australian techniques. With an α level of 5%, adjusted for multiple comparisons and power of 80%, it was calculated that 360 participants would be required, 120 in each of the three groups. Thus, 125 participants per group were recruited as, from our previous study,[14] a "drop out" rate of less than 4% was expected.

Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC, USA), based on a modified intention-to-treat population (ie, excluding children who did not return for follow-up). Multivariate logistic regression analysis was performed for each reaction parameter, with the outcome classified into no reaction (VAS score 0) and any reaction (VAS scores 1–5). Age and technique groups were included as factors in the model, together with their interaction. When there were small sample sizes in any one cell (eg, bruising), a Fisher's Exact Test was also used. A non-parametric Kruskal–Wallis test was used to compare parental acceptability, treated as a continuous varia-

2 Local and systemic adverse reactions by technique (Australian, World Health Organization and United States)

Reaction/vaccination/technique	Any reaction (score 1–5) No. (%)	Overall *P*	Australian v WHO technique / US v WHO technique Odds ratio (95% CI)	*P*
Redness/swelling				
Infanrix/InfanrixHepB		0.0752*		
Aust	31/121 (25.6%)		0.655 (0.370–1.158)	0.1458
WHO	40/120 (33.3%)			
US	46/120 (38.3%)		1.253 (0.730–2.150)	0.4133
Pedvax		0.1365*		
Aust	10/121 (8.3%)		0.800 (0.322–1.989)	0.6308
WHO	11/120 (9.2%)			
US	18/120 (15.0%)		1.773 (0.784–4.015)	0.1687
Bruising				
Infanrix/InfanrixHepB		0.0418*†		
Aust	3/121 (2.5%)			0.6219†
WHO	1/120 (0.8%)			
US	8/120 (6.7%)			0.0356†‡
Pedvax		0.3296*†		
Aust	0			1.0000†
WHO	1/120 (0.8%)			
US	2/120 (1.7%)			0.4979†
Systemic reactions				
Infanrix/InfanrixHepB/Pedvax				
Irritability		**0.0039***		
Aust	55/121 (45.5%)		1.969 (1.147–3.379)	**0.0139**
WHO	36/120 (30.0%)			
US	59/120 (49.2%)		2.437 (1.417–4.192)	**0.0013**
Perceived fever		0.3103		
Aust	4/121 (3.3%)		0.422 (0.126–1.409)	0.1605
WHO	9/120 (7.5%)			
US	9/120 (7.5%)		1.000 (0.383–2.613)	1.0000
Persistent crying/screaming		0.5162*		
Aust	10/121 (8.3%)		0.638 (0.270–1.505)	0.3042
WHO	15/120 (12.5%)			
US	14/120 (11.7%)		1.000 (0.452–2.212)	1.0000
Drowsiness		0.9428		
Aust	6/121 (5.0%)		1.200 (0.356–4.043)	0.7686
WHO	5/120 (4.2%)			
US	6/120 (5.0%)		1.210 (0.359–4.079)	0.7579
Vomiting/poor feeding		0.8118		
Aust	13/121 (10.7%)		1.083 (0.473–2.481)	0.8498
WHO	12/120 (10.0%)			
US	10/120 (8.3%)		0.818 (0.339–1.973)	0.6551

* Adjusted *P* value, after controlling for age in the model.
† *P* values calculated using Fisher's Exact test; all others derived from logistic regression analysis.
‡ Not statistically significant at $\alpha = 0.025$ (adjusting for multiple comparisons). ◆

ble on a scale of 0–5 (very happy to very unhappy) across the three technique groups.

RESULTS

A total of 375 consecutive children were enrolled in the study, all satisfying the inclusion criteria at presentation. The reason for unavailability of all 14 children who could not be evaluated 24 hours after vaccination was parental non-compliance rather than adverse effects. This was ascertained in follow-up contact by the practice nurse. The study groups were similar in terms of numbers per age group for the three techniques (Box 1).

No statistically significant interaction was found between technique and age in any of the logistic regression models, so this interaction factor was removed from the analysis model. Where the age factor was not significant, it was also removed from the analysis model. Age was significant in the analysis of redness/swelling, bruising, irritability and persistent crying, and was kept in these models. In Box 2, the *P* values for these parameters represent the significance of the test after adjusting for age.

The WHO technique resulted in significantly fewer patients with the systemic adverse reaction variable "irritability" (30.0%) compared with the Australian technique (45.5%) and the US technique (49.2%) ($P = 0.0039$). There was a significant difference between the groups overall for bruising with acellular pertussis vaccine ($P = 0.0418$) after controlling for age. The difference was due to 6.7% bruising for the US technique compared with 0.8% for the WHO technique ($P = 0.0356$), but this was not statistically significant at the $\alpha = 0.025$ level after adjusting for multiple comparisons (Box 2).

Most parents recorded parental acceptability scores of zero ("very happy"), the highest score being "3" recorded by one parent in the Australian technique group, and there were scores of "2" in the other two groups. The mean (95% CI) parental acceptability scores were 0.34 (0.23–0.45) for the Australian technique, 0.30 (0.20–0.38) for the WHO technique and 0.41 (0.30–0.52) for the US technique. There were no statistically significant differences in parental acceptability between the three techniques ($P = 0.2927$).

DISCUSSION

Ascertaining the best technique for paediatric vaccination is mandated by increasing concern about vaccine-induced adverse

reactions[15] in the context of a decreasing incidence of vaccine-preventable diseases. This concern is highlighted in a recent Australian study of children with incomplete vaccination, in which it was found that 70% of those who disagreed with or were concerned about immunisation had concerns about adverse reactions.[16]

In our study, the WHO technique was associated with fewer children having the adverse reaction "irritability" than with the other techniques and, for the acellular pertussis vaccine, less bruising compared with the US technique.

This outcome does not support the hypothesis (underpinning the US and Australian techniques) that angling of the needle to the long axis of the femur with intramuscular injection in children gives less adverse reactions.

The conclusion on the needle length aspect of vaccination practice by Diggle and Deeks[11] was weakened by the use of needles with different gauges (23 gauge/25 mm v 25 gauge/16 mm). Similarly, the inability to control needle length and gauge as potential variables in our study may have weakened the conclusions drawn regarding differences between the different techniques of injection. Our choice of needles was dictated by the recommendation of 23 gauge/25 mm long needles with the US[4] and Australian[5] technique and previous ultrasound studies[8,9] showing that 25 mm long needles would routinely make bony contact if used with the WHO technique. Elimination of needle gauge as a possible confounding variable was not possible, as 23 gauge/16 mm long needles are not commercially available.

The WHO technique best fulfils the requirements of an optimal injection technique in children — it ensures that the injection is intramuscular, results in fewer adverse reactions, and is the easiest technique to perform, as it does not require angling of the needle to the long axis of the femur.

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COMPETING INTERESTS

None identified.

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