

## Effect of needle size on immunogenicity and reactogenicity of vaccines in infants: randomised controlled trial

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### Abstract

**Objectives** To assess the immunogenicity of vaccines for infants and to investigate whether the incidence of reactogenicity is reduced after each immunisation dose using needles of varying lengths and gauges.

**Design** Randomised controlled trial.

**Setting** 18 general practices within two UK primary care trusts.

**Participants** 696 healthy infants vaccinated at 2, 3, and 4 months of age, with follow-up to 5 months of age.

**Interventions** Combined diphtheria, tetanus, whole cell pertussis, and *Haemophilus influenzae* type b vaccine and a serogroup C meningococcal glycoconjugate vaccine administered using either a wide, long needle (23 gauge/0.6 mm diameter, 25 mm), a narrow, short needle (25 gauge/0.5 mm diameter, 16 mm), or a narrow, long needle (25 gauge, 25 mm).

**Main outcome measures** Local and general reactions recorded by parents for three days after each dose; and diphtheria, tetanus, and *H influenzae* type b antibody concentrations and functional antibody against serogroup C *Neisseria meningitidis* 28-42 days after the third dose.

**Results** Local reactions to diphtheria, tetanus, whole cell pertussis, *H influenzae* type b vaccinations decreased significantly with wide, long needles compared with narrow, short needles. At all three doses one less infant experienced local reactions at days 1, 2, or 3 for every six to eight vaccinated. Significantly fewer infants vaccinated with the long needle experienced severe local reactions. Non-inferiority of the immune response was shown using a wide, long needle rather than a narrow, short needle for serogroup C meningococcal glycoconjugate vaccine and for diphtheria but not for *H influenzae* type b or tetanus, although no evidence was found of a decrease. Little difference was found between needles of the same length but different gauges in local reaction or immune response.

**Conclusions** Long (25 mm) needles for infant immunisations can significantly reduce vaccine reactogenicity at each dose while achieving comparable immunogenicity to that of short (16 mm) needles.

**Trial registration** Current Controlled Trials ISRCTN62032215.

### Introduction

Within UK general practices infants are immunised at 2, 3, and 4 months of age.<sup>1</sup> Despite recommendations for use of a 25 mm blue hub (23 gauge) needle,<sup>2</sup> many practitioners immunise using a 16 mm orange hub (25 gauge) needle and uncertainty has arisen because of insufficient data to define best practice.

We compared three needles of varying sizes and we assessed immunogenicity and reactogenicity after immunisation with a combined diphtheria, pertussis, tetanus, and *Haemophilus influenzae* type b vaccine and a meningococcal C vaccine. We aimed to test whether immunogenicity using a wide, long needle is equivalent or superior to a narrow, short needle (non-inferiority hypothesis).

### Methods

Eighteen of 35 general practices in two primary care trusts recruited infants due to receive their first immunisation (see [bmj.com](http://bmj.com) for exclusions). The first vaccination was at age 8-11 weeks, with subsequent vaccinations every 4-6 weeks.

Infants were allocated to a needle group according to a computer generated randomisation scheme, stratified by general practice. The study nurse allocated the next participant number and opened the appropriate numbered opaque envelope to determine needle group: wide, long (23 gauge, 25 mm), narrow, short (25 gauge, 16 mm), or narrow, long (25 gauge, 25 mm). Infants received all immunisations through the allocated needle.

A combined diphtheria, pertussis, tetanus, and *Haemophilus influenzae* type b vaccine was administered into the right thigh concomitantly with a meningococcal C vaccine into the left thigh, with the needle

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Local reactions according to needle size are on [bmj.com](http://bmj.com)



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inserted at 90° and using the intramuscular injection technique advocated by the World Health Organization (see [bmj.com](http://bmj.com)).<sup>3</sup> Parents were not told the needle size.

Parents completed a diary on reactions after each immunisation; the diameter of any redness, hardness, or swelling; the infant's reactions to movement of the thigh or touch of the injection site (none, mild, moderate, or severe); temperature; use of analgesics; and general reactions. A blood sample was obtained 28-42 days after the third vaccine dose.<sup>4 5</sup> During double data entry operators were blind to the needle allocations.

We measured specific serum immunoglobulin G against *H influenzae* type b and against tetanus, serogroup C meningococcal strain C11, and diphtheria antitoxin antibody levels. Laboratory staff were blinded to the allocation group.

Primary end points were geometric mean titres of meningococcal C antibodies and geometric mean concentrations of diphtheria, tetanus, and *H influenzae* type b antibodies 28-42 days after the third vaccine dose. Secondary end points were rates of any local reaction at both injection sites the evening after vaccination (six hours) and subsequent three evenings (days 1, 2, and 3) after each immunisation, as assessed by parents. Incidence of general reactions was also recorded. We express comparisons between needle groups as relative geometric mean titres or geometric mean concentrations for immunogenicity outcomes and as risk ratios for reactogenicity outcomes.

### Statistical analysis

The trial was designed to test the hypothesis that immunogenicity after use of the wide, long needle was no lower than that after the narrow, short needle. We pre-stated an equivalence bound of a relative reduction in geometric mean titres or geometric mean concentrations of 10%, above which differences would be interpreted as non-inferiority. We assessed statistical significance using one tailed *t* tests on log transformed data, computing the area in the left tail beyond the 10% equivalence bound. Significance was defined at the 2.5% level. We used confidence intervals calculated from the *t* distribution to compute the probability that an immune response was not inferior.<sup>6</sup>

To distinguish whether difference in length or gauge affected local reaction rates, we compared local reactogenicity rates between wide, long and narrow, short needles and between wide, long and narrow, long needles. We used two tailed  $\chi^2$  tests to test the significance of differences in reaction rates. Significance was defined at the 5% level. Differences in systemic reaction rates between the groups were tested using a  $\chi^2$  test with two degrees of freedom (or Fisher's exact test if event rates were low).

### Results

Of 696 infants enrolled, 240 were randomised to the wide, long needle, 230 to the narrow, short needle, and 226 to the narrow, long needle; the groups did not differ substantially at each vaccination (see [bmj.com](http://bmj.com)). Overall, 84 infants (12%) were withdrawn from the study (see [bmj.com](http://bmj.com)).

#### Wide, long needle versus narrow, short needle

**Immunogenicity**—The average immune response was higher with the wide, long needle than with the narrow, short needle, although none of the differences were significant (table). The largest increase was with the meningococcal C vaccine where the geometric mean titre increased by 30% (95% confidence interval –1% to 69%). Significant non-inferiority of response was shown for meningococcal C and diphtheria (see [bmj.com](http://bmj.com)). The probability that immune response using the wide, long needle was not inferior was estimated at 84% for *H influenzae* type b and 90% for tetanus.

**Local reactogenicity to combined vaccine**—On average 61% (388) of the infants experienced local reactions to each dose of combined vaccine (see [bmj.com](http://bmj.com)). The wide, long rather than the narrow, short needle was associated with significantly fewer local reactions for all three doses (figure), with relative reductions of between 22% (6% to 36%) and 54% (20% to 73%). At the six hour assessment relative reductions were smaller—5% (–12% to 20%) to 11% (–1% to 21%), and not statistically significant. Overall reaction rates were dominated by the high reaction rate at six hours and showed a significant reduction for the first dose only (see [bmj.com](http://bmj.com)). Significant reductions were, however, found with the wide, long needle in reactions evident the second day

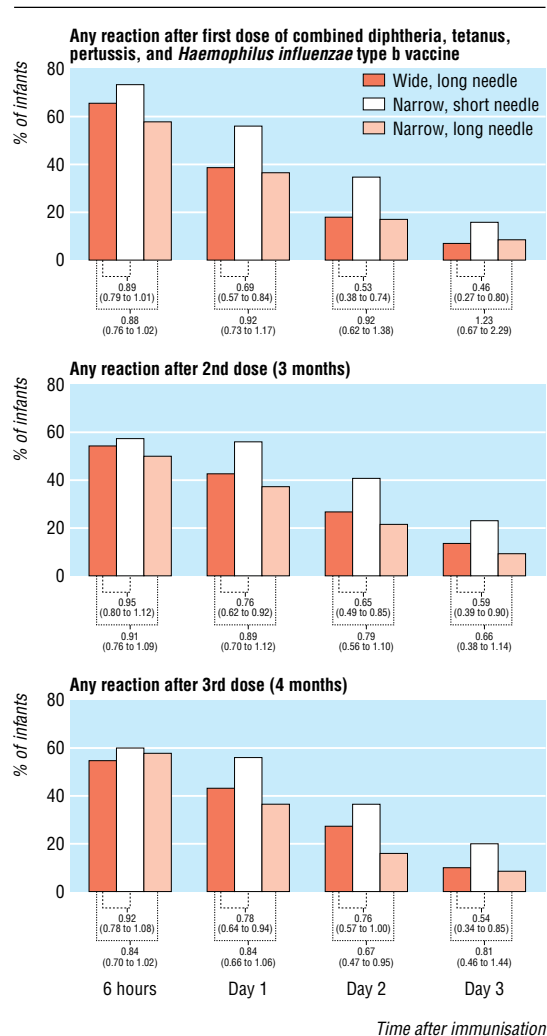
Vaccine immunogenicity in infants randomised to receive immunisations through one of three needle sizes

Variable	Geometric mean concentration or geometric mean titre by needle size (95% CI)			Ratio of geometric mean concentration or geometric mean titre (95% CI)*	
	Wide, long needle n=196	Narrow, short needle n=179	Narrow, long needle n=189	Wide, long v narrow, short needle	Narrow, long v wide, long needle
Meningococcal C vaccine†	1262 (1052 to 1514)	973 (799 to 1184)	1169 (972 to 1405)	1.30 (0.99 to 1.69)	0.93 (0.72 to 1.20)
SD (log)	1.29	1.28	1.33	—	—
<i>Haemophilus influenzae</i> type b	3.47 (2.82 to 4.28)	3.30 (2.65 to 4.12)	4.47 (3.76 to 5.32)	1.05 (0.78 to 1.42)	1.29 (0.98 to 1.69)
SD (log)	1.52	1.26	1.56	—	—
Tetanus	1.71 (1.51 to 1.93)	1.68 (1.47 to 1.93)	1.63 (1.44 to 1.84)	1.01 (0.84 to 1.22)	0.96 (0.80 to 1.14)
SD (log)	0.90	0.88	0.96	—	—
Diphtheria	0.24 (0.21 to 0.28)	0.21 (0.18 to 0.25)	0.22 (0.20 to 0.26)	1.13 (0.91 to 1.39)	0.93 (0.76 to 1.14)
SD (log)	0.95	0.85	0.93	—	—

SD (log)=standard deviation of measurements on natural log scale.

\*Statistically significant non-inferiority corresponds to lower limit of 95% confidence interval exceeding 0.90.

†Serogroup C meningococcal glycoconjugate vaccine.



Rates of local reactions using three sizes of needles for immunisations in infants. Values are relative risks (95% confidence intervals)

or later with relative reductions of 31% (16% to 44%), 24% (8% to 38%), and 24% (8% to 37%) for the first, second, and third doses. The number of infants needed to vaccinate with a wide, long rather than a narrow, short needle to prevent such a reaction are 6, 8, and 8 for the three doses. Of 11 infants withdrawn due to extensive redness and swelling, 10 were vaccinated using the narrow, short needle.

**Local reactogenicity to meningococcal C vaccine**—Reaction rates to the meningococcal C vaccine were lower than to the combined vaccine. On average 42% (262) of participants experienced local reactions to each dose of the vaccine. In total, 38% (240) showed a reaction six hours after vaccination, 23% (157) one day later, 11% (67) two days later, and 5% (32) three days later. No significant differences were noted between groups in overall reaction rates or reactions evident the second day or later (see bmj.com).

**Systemic reactogenicity**—No significant differences were found between the groups of infants with fever after any vaccine dose. Overall analgesic use and incidence of systemic reactions did not differ significantly between groups (see bmj.com).

### Narrow, long needle versus wide, long needle

No significant differences were found in immunogenicity between the two longer needles (table). Local reaction rates seemed slightly lower with the narrow needle, although differences were small and only reached significance for the overall rates of reaction for the third dose of the combined vaccine (see bmj.com) and rates on day 2 for the third dose (figure). No difference was found in systemic reactogenicity (see bmj.com).

### Discussion

The incidence of any local reaction after each immunisation dose in the UK schedule for infants aged 2, 3, and 4 months is significantly reduced when a wide, long (25 mm) needle rather than a narrow, short (16 mm) needle is used. Although only two of the four vaccine components showed non-inferiority, the weight of evidence favoured the wide, long needle, achieving comparable, if not superior, immunogenicity to that of the narrow, short needle.

This study also provides evidence that needle length, rather than gauge, is associated with reduced reactogenicity. Some authors suggested that the narrower 25 gauge needle might produce an injection jet under pressure, which causes increased trauma and local reaction rates.<sup>7,8</sup> We observed little difference between needle gauges.

We suggest that the longer needle ensures delivery into an infant's thigh muscle. Several trials of vaccines in adults or adolescents have shown that intramuscular delivery minimises adverse reactions,<sup>9,10</sup> and a clear physiological rationale justifies its importance; poorer drainage channels in subcutaneous tissue may make subcutaneous fat more susceptible to the adverse effects of vaccines.<sup>11</sup> Intramuscular delivery is particularly recommended for vaccines containing aluminium adjuvant, as inadvertent subcutaneous administration may increase irritation or lead to lumps at the injection site.<sup>12</sup> As injection with a 16 mm needle inserted at 90° has been shown not to reach muscle in a significant number of infants aged 4 months,<sup>13</sup> and as the combined diphtheria, pertussis, tetanus, and *Haemophilus influenzae* type b vaccine contains aluminium adjuvant, this may explain differences in reactogenicity between needle lengths in our study.

The mechanism by which intramuscular delivery of vaccines contributes towards improved immunogenicity has been described.<sup>14</sup> Compared with subcutaneous tissue, muscle has an abundant blood supply.<sup>14</sup> In studies of adults, intramuscular delivery provided significantly improved seroconversion.<sup>14,15</sup> Our study provided some evidence that for meningococcal C vaccine the longer needle provided a better immunological response.

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**What is already known on this topic**

At age 4 months a wide, long rather than narrow, short needle for immunisation reduces local reaction

Whether this was due to needle length or gauge or could be achieved at younger immunisation ages was unknown

Effect on immunogenicity was unknown

**What this study adds**

Long (25 mm) needles provide the optimum immunisation at 2, 3, and 4 months of age

Needle length, not gauge, affects reactogenicity

Immunogenicity is comparable between long and short (16 mm) needles

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Competing interests: LD has received assistance from Wyeth Vaccines and Sanofi Pasteur MSD to attend scientific meetings. AJP acts as chief investigator for clinical trials conducted on behalf of Oxford University, sponsored by vaccine manufacturers (Sanofi-Pasteur MSD, Novartis Vaccines, GlaxoSmithKline, Sanofi-Pasteur, and Wyeth Vaccines), and has received

assistance from GSK vaccines, Sanofi Pasteur MSD, Novartis Vaccines, and Wyeth Vaccines to attend scientific meetings. AJP is an inventor on a patent application in the area of meningococcal B vaccines. Industry sourced consultancies or honorariums are paid directly to an independent charity or an educational fund held by the Department of Paediatrics, University of Oxford.

Ethical approval: This study was approved by the Mid and South Buckinghamshire and Oxfordshire local research ethics committees.

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*A memorable patient*

**Seeing the message**

All NHS patients attending hospital have their religion diligently documented in a box somewhere in the case notes, but we tend to forget that sometimes our patients' beliefs are more important for them than anything we might be able to offer.

I recall clerking an anxious patient admitted for coronary artery bypass grafting and being surprised that he was in deep discussion with the hospital priest. I settled down to complete his "integrated care pathway" but, having asking four questions, I decided to abandon ward protocol and asked him why he had felt the need to consult a priest. He admitted that he was afraid of what lay ahead and feared that his operation would be less successful than he had been led to believe. Certainly he was a high risk candidate: this was his second heart operation, he had ongoing unstable symptoms, he was diabetic, and had been quoted a 20% mortality risk from the operation.

Fearing that he might cancel his operation and discharge himself, I reassured him as best as I could about the more likely positive outcome of his operation and stressed the risk of sudden

death from heart failure at any moment were he to walk out. After a long discussion, he agreed to stay, and I was relieved to see his bed being wheeled to theatre the following morning.

Postoperatively, he was taken to theatre again with a heavy suspicion of tamponade. He did not respond to further treatment and died that night, having never regained consciousness. The first I knew of this was the empty bed that faced me the next day.

I was surprised at how guilty I felt, and I suddenly realised that the real surprise was not that this one patient had weighed on my conscience but that hundreds of others had not. As doctors, we see patients' self discharge as a failure on our part, but we seldom get to grips with the underlying reasons. Sometimes we come across a patient who seems to have a message just for us; but the real challenge is seeing the message in every patient.

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