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

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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 antibodies determined at days 1, 2, or 3 for every six to eight vaccinated infants.

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 infants. 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.1 Despite recommendations for use of a 25 mm blue hub (23 gauge) needle,2 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 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 (23 gauge, 25 mm), narrow, short (25 gauge, 16 mm), or narrow, long (25 gauge, 25 mm).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean concentration or geometric mean titre by needle size (95% CI)</th>
<th>Ratio of geometric mean concentration or geometric mean titre (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wide, long needle</td>
<td>Narrow, short needle</td>
</tr>
<tr>
<td>Meningococcal C vaccine†</td>
<td>1262 (1052 to 1514)</td>
<td>973 (799 to 1184)</td>
</tr>
<tr>
<td>SD (log)</td>
<td>2.39</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>n=196</td>
<td>n=179</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>3.47 (2.82 to 4.28)</td>
<td>3.30 (2.65 to 4.13)</td>
</tr>
<tr>
<td>SD (log)</td>
<td>0.20</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>n=208</td>
<td>n=194</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1.71 (1.51 to 1.93)</td>
<td>1.66 (1.47 to 1.85)</td>
</tr>
<tr>
<td>SD (log)</td>
<td>0.90</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>n=203</td>
<td>n=191</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>0.24 (0.21 to 0.28)</td>
<td>0.21 (0.18 to 0.25)</td>
</tr>
<tr>
<td>SD (log)</td>
<td>0.95</td>
<td>0.85</td>
</tr>
</tbody>
</table>

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.

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 prestated an equivalence bound of a relative reduction (95% confidence interval) ≤ 0.90 from the wide, long needle in reactions evident the second day (see bmj.com).

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). Overall, 84 infants (12%) were withdrawn from the study (see 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 statistically 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%). Non-inferiority of response was shown for meningococcal C and diphtheria (see 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). 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). Significant reductions were, however, found with the wide, long needle in reactions evident the second day.
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. 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 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. 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. 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, 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. Compared with subcutaneous tissue, muscle has an abundant blood supply. In studies of adults, intramuscular delivery provided significantly improved seroconversion. Our study provided some evidence that for meningococcal C vaccine the longer needle provided a better immunological response.

We thank the participants; research nurses Karen Stone, Helen Layton, and Tessa Waterhouse for carrying out the study visits, administering immunisations, and collecting venepuncture samples; Shamim Shah-Gallardo for distraction of infants during venepuncture; general practices of Vale of Aylesbury and North East Oxfordshire primary care trusts who participated and welcomed us into their surgeries; Vale of Aylesbury and Oxfordshire child health computer departments for mailing of invitation letters to parents; Ray Borrow and team (Health Protection Agency Meningococcal Reference Unit, Manchester Royal Infirmary) for meningococcal C serum analyses; Armelle...
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 clerk 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 asked 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 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 appeared across a patient who seems to have a message just for us; but the underlying reasons. Sometimes we come to see patients’ self discharge as a failure on our part, but we seldom consider the conscience but that hundreds of others had not. As doctors, we are all taught to be intrinsically aware of our own mortality, but few are aware that 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.

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