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Immunological response to conjugate vaccines in infants: follow up study

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Immunising infants against *Haemophilus influenzae* type b with conjugate vaccines has reduced rates of invasive disease in the developed world. Reports from the Gambia suggest that this vaccine has a similar potential for the developing world.[1] The World Health Organisation is considering whether to provide these new vaccines as part of its expanded programme of immunisation.[2]

A booster dose of the conjugate vaccine administered in the second year of life is generally considered necessary to induce long term immunity against *H influenzae* type b. This may limit the use of these conjugate vaccines in the developing world where vaccines are administered at 6, 10, and 14 weeks of age under the WHO's immunisation programme; delivery of further vaccinations are associated with logistical problems. In the United Kingdom, infant immunisation takes place in an accelerated fashion at 8, 12, and 16 weeks of age and no booster dose of the conjugate vaccine is administered. Evidence of the effectiveness of this schedule has been published,[3] but its success in the United Kingdom may be related to the immunisation of all children younger than 5 years of age; this mass immunisation may have abruptly reduced nasopharyngeal carriage and modes of transmission.

To evaluate the effectiveness of the accelerated immunisation schedule in the United Kingdom we investigated whether the schedule primed infants' immune systems for memory responses at the age of 1 year.

Subjects, methods, and results

This study is a follow up of a previously reported study of the interchangeability of two conjugate vaccines against *H influenzae* type b.[4] Infants whose immune systems had been primed with a conjugate vaccine administered with diphtheria, tetanus, and pertussis vaccines at 2, 3, and 4 months of age received one of two conjugates, either ActHIB (Pasteur-Mérieux-MSD, Lyon) or HibTITER (Cyanamid-Lederle-Praxis Biologicals, Pearl River, USA) at the age of 1 year. *H influenzae* type b polysaccharide (polyribosylribitol-phosphate) IgG titres were estimated by enzyme linked immunosorbent assay after primary immunisation, and then immediately before and 1 month after the booster dose was administered.

Altogether 516 infants were recruited. Serum samples were obtained from 401 infants before they received a booster dose and 387 infants after they

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received a booster dose. *H influenzae* type b polysaccharide IgG responses are shown in the table. The proportions of children who had antibody titres below the minimum protective level of 0.15μg/ml before receiving their booster dose at 1 year of age was higher than previously reported with the more extended primary immunisation schedule.[5] The mean increase in antibody titre after administration of the booster dose was 803-fold (95% confidence interval 651 to 955).

Comment

This increase in antibody titres after booster immunisation is consistent with an immunological memory response, and shows that the children's immune systems were successfully primed by the three doses of conjugate vaccine they received during infancy. Immunological memory induced by vaccines administered according to the accelerated primary schedule may provide long term protection even when circulating antibody titres are low. Conjugate vaccines against *H influenzae* type b could be introduced into the expanded immunisation programme of the WHO using a schedule of three doses in infancy and no booster dose. This should enhance deliverability and reduce costs.

Geometric mean titre (95% confidence interval) of *Haemophilus influenzae* type b polysaccharide IgG, and the number (percentage) of infants with antibody titres below the minimum protective concentration (0.15μg/ml) or above the long term protective concentration (1.0μg/ml) after primary immunisation with three doses of conjugate vaccine, and immediately before and 1 month after a booster dose of the vaccine given at 1 year of age

			Antibody titre	
	No	Geometric mean titre	<0.15μg/ml	>1.0μg/ml
After primary immunisation	516	6.23 (5.53 to 7.01)	10 (2)	478 (93)
Immediately before booster dose	401	0.41 (0.35 to 0.47)	153 (38)	126 (31)
1 month after booster dose	387	108.39 (91.62 to 128.23)	7 (2)	380 (98)

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Initiatives to improve childhood immunisation uptake: a randomised controlled trial

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Levels of childhood immunisation are high in the United Kingdom but are proving difficult to maintain. Several initiatives to improve uptake have been described, including sending written information to parents,[1] specialist immunisation clinics,[2] and prompts to health visitors and general practitioners.[3] However, none of these interventions has been the subject of a randomised controlled trial. We tested the effectiveness of two such interventions.

Subjects, methods, and results

The child health system, which maintains computerised data on immunisation status of all children, was used as the sampling frame. The study population comprised children resident in the former county of South Glamorgan who were (*a*) born between 1 April and 30 September 1995 and scheduled to complete the primary course of diphtheria, pertussis, tetanus, polio, and *Haemophilus influenzae* type b immunisation or (*b*) born between 1 April and 30 September 1994 and scheduled to receive measles, mumps, and rubella immunisation. Children were included in the trial if they had not completed their primary course by 9 months of age or their measles, mumps, and rubella immunisation by 21 months of age.

Each week between 1 January and 30 June 1996 we received a computer generated list of children eligible for inclusion in the study and randomised each child using computer generated random numbers to one of two interventions or a control group. Intervention A comprised a non-directive telephone call to the child's health visitor to confirm the child's personal details and immunisation status. The health visitor was not informed of the trial and, although follow up of the child was anticipated, it was not specifically requested. Intervention B comprised a single mailed reminder to the child's parents together with a questionnaire about details of immunisation status and reasons for non-immunisation, and a reply paid envelope. Parents were not informed of the trial.

Study end points were completion of (*a*) primary immunisation by the first birthday or (*b*) measles, mumps, and rubella immunisation by the second birthday. We performed statistical analysis on an intention to treat basis, using the χ^2 test with Yates's correction for baseline comparisons, and calculated 95% confidence intervals for the difference in proportions.