

Short reports

Pyrexia after diphtheria/tetanus/pertussis and diphtheria/tetanus vaccines

P A WAIGHT, T M POLLOCK, E MILLER, AND E M COLEMAN

Epidemiological Research Laboratory, Central Public Health Laboratory, London, and Dorset Area Health Authority

SUMMARY The temperatures of 587 children were taken before and after diphtheria/tetanus/pertussis (DTP) or diphtheria/tetanus (DT) vaccine. Only slight temperature increases were found but these were notably more frequent after plain than adsorbed DTP vaccine preparations and the frequency increased with each successive dose.

The frequent occurrence of high fever after diphtheria/tetanus/pertussis (DTP) vaccine sometimes associated with febrile convulsions has been reported in the USA.^{1,2,3} We compared the axillary temperatures of young British children before and after vaccination with either DTP or diphtheria/tetanus (DT) vaccine. Local reactions to each vaccine were also recorded.

Participants and methods

We studied 587 infants attending local health authority clinics in Dorset for their first, second, or third dose of vaccine in the course of routine primary immunisation. During the study, 401 children had one dose of either DTP or DT vaccine, 151 had two doses, and 35 had a full course of three injections. Temperatures were therefore taken before and after 808 doses of vaccine. All the DT vaccine and most of the DTP vaccine were adsorbed preparations, but for 43 of the DTP doses a plain preparation was used. Each of the vaccines was prepared by the same manufacturer (Wellcome). Temperatures were taken by one of us (E M C), immediately before vaccination at the clinic and then in the infants' homes four hours or 20-24 hours, or both, later. Care was taken to ensure that the thermometer was held firmly in the axilla and remained in place for two minutes. The diameters of any erythema occurring at the site of injection were measured with a ruler and the presence and degree of swelling were recorded.

Results

Temperatures. Only mild temperature increases were

found and for the purposes of the study fever was defined as an axillary temperature of 37.5°C or more. Four of the 808 prevaccination temperatures were greater than 37.5°C and showed no post-vaccination increases. These four (five postvaccination temperature readings) have been excluded from the study. Only four of the 283 temperatures (1%) taken at 4 hours in DTP vaccinated children were more than 37.5°C. The temperature increases were slight and none of the children with fever at 4 hours still had fever at 20-24 hours. These 4 hour fevers all followed adsorbed DTP vaccine. No temperatures greater than 37.5°C were found 4 hours after DT.

Fever was more frequent at 20-24 hours after DTP than at 4 hours, was more common after plain than after adsorbed DTP vaccine (Table), but was mild after both preparations (Figure). After adsorbed DT vaccine, fever was infrequent (Table).

As might be expected, fever was more frequent when the postvaccination temperature was taken in the afternoon or evening than in the morning. The

Table *Instances of fever ($\geq 37.5^{\circ}\text{C}$) 20-24 hours after vaccination with plain or adsorbed diphtheria/tetanus/pertussis (DTP) or adsorbed diphtheria/tetanus (DT) vaccine*

Vaccine	Dose	Total temperature readings	Fever	
			No	(%)
Adsorbed DTP	1st	92	1	(1)
	2nd	112	1	(1)
	3rd	128	6	(5)
Total		332	8	(2)
Plain DTP	1st.	12	0	(0)
	2nd	16	2	(12)
	3rd	12	6	(50)
Total		40	8	(20)
Adsorbed DT	1st	67	0	(0)
	2nd	80	1	(1)
	3rd	74	1	(1)
Total		221	2	(1)

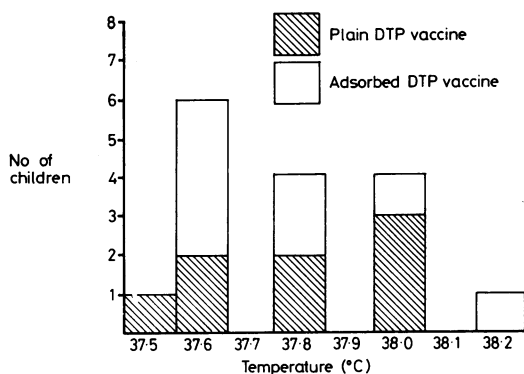


Figure Temperatures of children with fever 20-24 hours after diphtheria/tetanus/pertussis (DTP) vaccination.

four fevers which occurred 4 hours after DTP vaccination were all observed in the evening. Among the 291 temperatures taken in the morning, 20-24 hours after DTP vaccination, were 9 fevers (3%). Among 81 afternoon readings, however, there were 7 fevers (9%).

Fever was more frequent after the third dose of DTP (Table). Six of the 12 infants who had had third doses (50%) of plain DTP vaccine, followed up at 20-24 hours, had fever—four of these were morning readings. In contrast, 6 of 128 infants who had had third doses (15%) of adsorbed DTP vaccine had a fever at 20-24 hours, and three of these temperatures were read in the morning.

Local reactions. There were no pronounced local reactions. Erythema greater than 2 cm in diameter was more common after plain DTP vaccine than adsorbed DTP vaccine (18% and 11%, respectively at 20-24 hours), and was least after DT (5%). With all three vaccines the proportion of children with erythema increased with each successive dose. Twenty to 24 hours after the third dose 20% of the infants receiving adsorbed DTP, 50% of those receiving plain DTP, and 15% of the DT vaccine recipients had erythema greater than 2 cm in diameter. Swelling was evident at 20-24 hours in 44% of adsorbed DTP vaccine recipients, 55% of plain DTP recipients, and 29% of those receiving DT. Like erythema, swelling also increased with each dose.

Discussion

The infrequency and mildness of the fever observed in these babies contrast with findings in two American studies. Cody *et al.*¹ reported fever of

38°C or more in 47% of children given DTP and 9% given DT. Moreover, maximum temperatures were found 3-6 hours after the injection. This also differed from the UK finding where the temperatures were greater at 20-24 hours. Barkin and Pichichero² reported that more than half of DTP immunised children had an increase in temperature within 48 hours, 4% having a temperature of 38°C or more.

There are differences between the American and British studies. In the former, no prevaccination temperature was measured, the postvaccination readings were taken by the parents instead of a single nurse, and the site from which the temperature was taken was not reported. In addition, the American children came from a much wider age range (0-6 years) and five doses of vaccine were given in America compared with three doses in the UK. Finally, although the source of the vaccines used in the American studies was not stated, they were presumably obtained from American manufacturers, while in the British study the vaccines were obtained from a single British source. Because of these variables, detailed conclusions cannot be drawn. Nevertheless, the differences seem large enough to suggest that fever is greater and occurs more often with American vaccine or schedules, or both, than with those in current use in the UK. Laboratory toxicity tests do not suggest notable differences between British and American DTP vaccines.⁴

Our findings suggest that an injection of adsorbed DTP vaccine may be slightly more likely to provoke an increase in temperature in the following 24 hours than an injection of DT. The likelihood of fever is, however, much greater when plain rather than adsorbed preparations of DTP are used, and the type of preparation should be stated when reactions to DTP vaccine are being discussed.

Mild fevers only were found in this study. Higher fevers within 24 hours of immunisation with DTP seem to be infrequent and their incidence may only be assessed by a much larger study. High fever after DTP may be caused by unusual susceptibility or by an acute infection at the time of vaccination. Fever and local reactions were most common after the third dose which, in the UK, is usually given at about age 10 months, a time when febrile convulsions become increasingly common.⁵ Although febrile convulsions after DTP are infrequent,^{3,5} their likelihood might be reduced if the third dose were given at an earlier age.

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Correspondence to Miss Pauline A Waight, Epidemiological Research Laboratory, Central Public Health Laboratory, Colindale Avenue, London, NW9 5HT.

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β cell function in siblings of diabetic children and HLA type

E SCHOBER, G SCHERNTHANER, H FRISCH, J BIEBER, AND W MAYR

Department of Pediatrics, Department of Medicine II, and Institute of Blood Group Serology, University of Vienna, and Ludwig Boltzmann Institute for Clinical and Pediatric Endocrinology, Pediatric Department of LKH Mödling

SUMMARY β cell function was tested in HLA-DR typed siblings of insulin dependent diabetic children. HLA identical siblings showed an increased insulin response compared with controls and HLA non-identical siblings. This β cell hyperactivity may be an early carbohydrate intolerance or a genetically determined increase in β cell metabolism.

Studies of HLA typing in families with more than one diabetic child show that siblings with HLA typing identical to the diabetic child have a high risk of developing insulin dependent diabetes (IDD). In recent investigations of IDD^{1 2 3} a long, clinically asymptomatic stage before any clinical manifestation of the disease has been shown. It is of interest, therefore, whether siblings with the highest genetic risk of IDD have an abnormal β cell function.

Patients and methods

Forty four families with one child with IDD and at least one sibling without IDD were included in the study. The age of the diabetic children (24 boys and 20 girls) was mean (SD) 11.8 (2.8) years, and that of their 66 non-diabetic siblings (37 boys and 29 girls) was mean (SD) 13.1 (3.4) years. An oral glucose tolerance test (OGTT) (glucose 1.75 g/kg) was performed between 8 and 10 am in all siblings, after overnight fasting. Blood samples, drawn using an indwelling needle at 0, 60, and 120 minutes, were centrifuged and frozen at -20°C until assay.

Control data were obtained from 33 healthy school-children with no family history of diabetes (age mean (SD) 13.9 (1.1) years).

Serum glucose values were measured by the glucose oxidase method and insulin determination was performed by radioimmunoassay. HLA-ABC typing was performed by means of a standard NIH lymphocytotoxicity technique and DR locus typing by the 2 colour fluorescence technique.

Informed written consent was obtained from the parents. For statistical analysis a non parametric test (U test) was applied.

Results

Nineteen children were HLA identical, 25 were haploidentical, and 22 were not HLA identical to their diabetic siblings. One boy, who did not have clinically apparent diabetes, had an abnormal OGTT, (blood glucose 13.3 mmol/l at 60 min and 18.1 mmol/l at 120 min). After fasting his blood glucose value (5.5 mmol/l) and immunoreactive insulin value (6.4 $\mu\text{U/ml}$) were normal, but the increase in the latter after the oral glucose load was low (24.7 and 28.4 $\mu\text{U/ml}$ at 60 and 120 minutes, respectively). The results of this child's tests were excluded from the analysis. He had both risk antigens for IDD—HLA-DR3 and HLA-DR4—and was haploidentical to his diabetic brother. All other siblings showed normal blood glucose values during the test.

The insulin response to the oral glucose load was