

A comparative clinical study of Adsorbed Tetanus Vaccine and Adult-type Tetanus–Diphtheria Vaccine

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SUMMARY

A limited assessment of immunity to diphtheria revealed that only 44·8% of adults had protective levels ($> 0\cdot01$ U/ml) of diphtheria antitoxin in their sera. In the light of this information, it was decided to assess the suitability of Adult-type Tetanus–Diphtheria Vaccine as a replacement for Adsorbed Tetanus Vaccine in occupational health schemes. A comparative study of these vaccines showed that a single dose of each produced an equivalent rate and level of tetanus antitoxin responses. Adult-type Td Vaccine elicited more than fourfold increases of diphtheria antitoxin in 76% of vaccinees. No statistically significant differences were observed in the clinical reactivity of the vaccines under test. However, the combined vaccine caused a slightly higher incidence of local reactions (pain, redness and swelling) while recipients of Adsorbed Tetanus Vaccine more frequently experienced pain.

INTRODUCTION

Recent serological surveys have shown that approximately half the working population in the United Kingdom do not have protective levels of diphtheria antitoxin in their sera (Ad-hoc Working Group, 1978; Mitchell & Barr, 1978). It would, therefore, appear desirable to include diphtheria immunization in occupational health schemes. Unfortunately, unselective immunization of adults is complicated by a high frequency of reactions (Pappenheimer *et al.* 1950) and the screening procedures required to exclude immune or sensitized individuals are inconvenient and time-consuming. In the context of occupational health, therefore, routine immunization against diphtheria would be practicable only if a combined tetanus and diphtheria vaccine could be used instead of tetanus vaccine. The combined vaccine would, of course, need to be no more reactive than tetanus toxoid alone. For this reason, it was decided to assess the suitability, for routine use, of Adult-type Td Vaccine (Edsall, Altman & Gaspar, 1954; Ipsen, 1954) which is an adsorbed tetanus–diphtheria vaccine containing reduced levels of diphtheria toxoid and normal levels of tetanus toxoid. The present study, performed in an occupational health setting, compares clinical reactions and serological responses

Table 1. *Age, sex and tetanus vaccination history of volunteers*

	Tet/Vac/Ads group	Td/Vac group
No. of volunteers	31	29
Mean age (years)	40	42
Age range (years)	19-54	25-57
No. male	21 (68%)	16 (55%)
No. given primary course of tetanus toxoid in 1969	24	20
No. subsequently given one dose tetanus toxoid	3	2
No. unvaccinated post-1968	4	7

following administration of a single dose of Adsorbed Adult-type Td Vaccine (Td/Vac) and Adsorbed Tetanus Vaccine (Tet/Vac/Ads).

MATERIALS AND METHODS

Sixty healthy Caucasian volunteers, aged 19-57 years, were recruited from employees at ICI, Blackley, Manchester during a routine tetanus immunization programme, and randomly assigned to receive a single 0.5 ml subcutaneous dose of either Adsorbed Tetanus Vaccine ($n = 31$) or Adult-type Td Vaccine ($n = 29$), administered by needle and syringe. There was no statistically significant difference between the two groups of volunteers with respect to age, sex or history of tetanus vaccination (see Table 1).

Vaccines

Monocomponent vaccine (Adsorbed Tetanus Vaccine, Wellcome) contained tetanus toxoid adsorbed onto aluminium hydroxide (10 Lf toxoid and 0.35 mg Al/dose) and had an immunizing potency of 112 IU/dose. Each dose of combined vaccine (Adult-type Td Vaccine, Wyeth) contained 10 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid adsorbed onto aluminium phosphate (0.37 mg Al/dose). The immunizing potency of this material against challenge with tetanus toxin was 205.8 IU/dose.

Serology

Blood (20 ml) was collected from volunteers immediately before and 5 weeks after vaccination. The titre of circulating tetanus antitoxin was determined by toxin neutralisation tests (Glenny & Stevens, 1938). All pre-vaccination and 58 post-vaccination sera were tested. Two subjects in the group receiving Adsorbed Tetanus Vaccine failed to provide blood samples after vaccination. The levels of diphtheria antitoxin were measured only in paired sera from subjects who had received Adult-type Td Vaccine. Diphtheria antitoxin levels were estimated by standard toxin neutralisation (Glenny & Allen, 1921).

Clinical reactions

Vaccinees were asked to complete a daily calendar record for 7 days after vaccination to report the occurrence and severity of local reactions (pain, redness

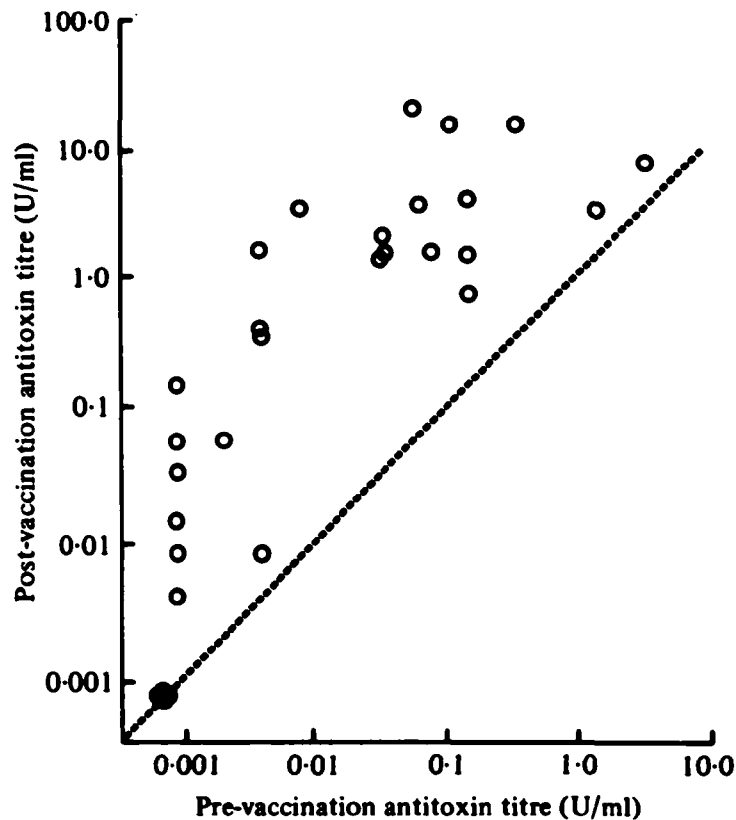


Fig. 1. Serum diphtheria antitoxin levels before and after vaccination with Adult-type Td Vaccine. Antitoxin titre < 0.01 U/ml = non-protected.

and swelling) and systemic reactions (headache, fever and myalgia). Local reactions were graded 1–3 according to whether they were mild, moderate or severe. In 39/60 instances the injection sites were examined 48 h after vaccination, when an assessment of the severity of erythema and swelling was made. The longitudinal and transverse diameters of erythema, if present, were recorded at that time. The remaining 21 vaccinees were not monitored because of difficulties in staff timing.

RESULTS

Serological response to vaccination

Diphtheria antitoxin

Diphtheria antitoxin levels were measured only in paired sera from volunteers in the Adult-type Td vaccine group. 20/29 volunteers, including nine subjects with pre-vaccination titres of < 0.01 U/ml, responded satisfactorily to vaccination, registering 5–750-fold increases in antitoxin titre (see Fig. 1). The geometric mean titre (GMT) for these subjects was 0.018 U/ml prior to vaccination and 1.42 U/ml thereafter. Two of the nine subjects with an inadequate response had antitoxin levels above 1.0 U/ml before vaccination and showed a twofold rise following vaccination. The remaining seven subjects, all susceptible to diphtheria (< 0.01 U/ml) before vaccination, failed to raise an antitoxin response to vaccination. 6/7 of these volunteers did not have a previous history of diphtheria vaccination.

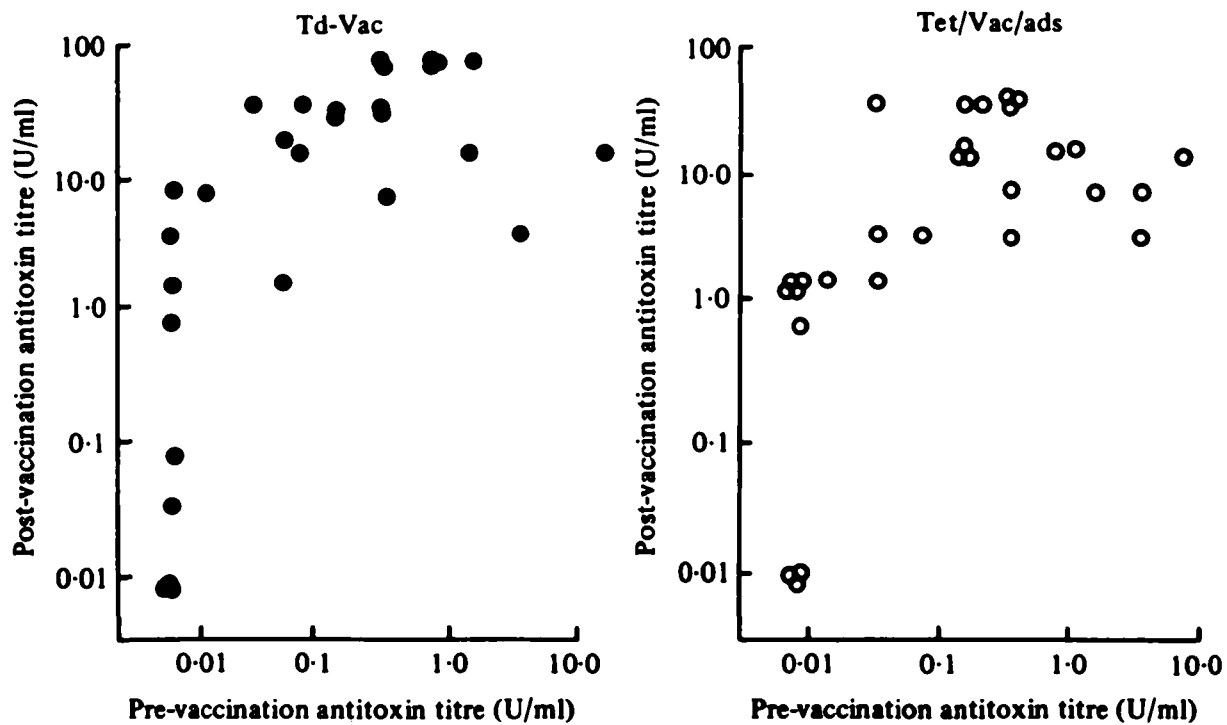


Fig. 2. Serum tetanus antitoxin levels before and after vaccination. ○ = Tetanus Vaccine Adsorbed; ● = Adult-type Td Vaccine; Antitoxin titre < 0.01 U/ml = non-protected.

Tetanus antitoxin

The serum tetanus antitoxin titres were measured on 58 paired sera – 29 pairs from each vaccine group. Antitoxin responses were very similar for the two preparations under test (see Fig. 2). In eight subjects, four in each group, with pre-vaccination antitoxin titres above 1.0 U/ml, the antitoxin titres were either unchanged after vaccination or showed only minimal rises. A further three vaccinees in each group, all with antitoxin titres of < 0.01 U/ml, failed to respond to vaccination, their antitoxin titres remaining at this non-protective level. The remaining subjects, including 12 subjects with pre-vaccination titres of < 0.01 U/ml, responded adequately to vaccination.

The post-vaccination titres of the sero-responders to Adsorbed Tetanus Vaccine ranged from 0.75 to 35 U/ml, with pre- to post-vaccination increases of 20–100-fold. The GMT of these post-vaccination sera was 6.99 U/ml as compared to 0.08 U/ml in pre-vaccination samples.

In comparison, the 22 sero-responders to Adult-type Td Vaccine attained levels of between 0.035 and 75 U/ml in the post-vaccination sera. These values represented 4–1000-fold increases in titre. The GMT was calculated as 7.25 U/ml after, as compared to 0.082 U/ml before, vaccination.

No statistically significant differences in the tetanus antitoxin response were observed for the two vaccines under test.

Clinical reactions

Local reactions

Inspection of the calendar record forms returned by all 60 vaccinees showed no statistically significant differences in reactivity between the groups (see Table 2). It is, however, interesting to note that the pattern of reactivity was dependent

Table 2. Clinical reactions recorded following vaccination

	Tet/Vac/Ads group	Td/Vac group	Statistical significance (<i>P</i> value)
No. in group	31	29	—
No. (%) of subjects reporting pain and/or redness and/or swelling on any day	21 (68%)	23 (79%)	0.47
No. (%) of subjects reporting concurrent redness and swelling on any day	19 (61%)	19 (66%)	0.84
No. (%) of subjects reporting pain on any day	13 (42%)	6 (21%)	0.14
No. (%) of observations of erythema	†9 (41%)	†10 (59%)	0.57
Mean area of erythema present (cm ²)	‡43.9	‡30.5	0.65
No. (%) of subjects recording systemic reaction	5 (16%)	3 (10%)	0.79

† These figures refer to those subjects whose arms were inspected ($n = 22$ for Tet/Vac/Ads and $n = 17$ for Td/Vac).

‡ These figures refer to those subjects in whom erythema was observed to be present.

on the vaccine administered. There was, for instance, a greater incidence of local reactions, after the administration of Adult-type Td Vaccine than after the administration of Adsorbed Tetanus Vaccine. In particular, erythema occurred at a lower frequency in the recipients of Adsorbed Tetanus Vaccine (41%) compared to Adult-type Td Vaccine (59%). Conversely, pain was reported more frequently by volunteers who received Adsorbed Tetanus Vaccine; 42% of the recipients of this vaccine recorded pain on one or more occasions, whereas only 21% of the recipients of Adult-type Td Vaccine made similar entries. The pain recorded by recipients of Adsorbed Tetanus Vaccine was also more prolonged with a mean duration of 3.30 days, as compared to 2.16 days. Although this difference failed to achieve statistical significance the overall mean duration of pain (sum of duration of pain/total number in group) was significantly greater ($P < 0.05$) in the group receiving Adsorbed Tetanus Vaccine.

Systemic reactions

Twelve reports of headache and/or feverishness and/or myalgia were made by volunteers in the study. Of these reactions four were experienced concurrently with 'other symptoms', such as upper respiratory tract infections or nausea. These reports have been omitted from the data in Table 2. Of the eight remaining volunteers recording reactions, three in each group reported headaches. Feverishness (two subjects) and myalgia (one subject) were also reported by recipients of Adsorbed Tetanus Vaccine. The only report of feverishness (experienced as the sole systemic symptom) was made on days 4–5 and was not accompanied by any local reaction. Otherwise systemic symptoms were accompanied by local reactions commencing between days 1 and 3 and, with one exception, lasted for 1 or 2 days. The exception (a headache of 4 day's duration) was experienced by a subject with

a tetanus antitoxin titre of 7.5 U/ml in the pre-vaccination serum. There were no major differences in the number, duration or severity of the reactions reported by volunteers in the different vaccine groups.

DISCUSSION

Adsorbed Tetanus and Adult-type Td Vaccines were equivalent in the rate and level of tetanus antitoxin responses elicited. With both vaccines, only three subjects failed to achieve protective antitoxin levels. Of these subjects, five did not report a history of tetanus vaccination and were probably primary vaccinees. The only previously vaccinated subject who failed to respond to tetanus toxoid raised an antitoxin response to simultaneously administered diphtheria toxoid. This subject may, therefore, represent one of the small group of individuals responding inadequately to tetanus vaccination (Scheibel, Bentzon & Christensen, 1966). One dose of either vaccine, however, provided adequate reinforcement of immunity to tetanus.

Adult-type Td Vaccine also appeared effective in boosting the diphtheria antitoxin levels of subjects previously primed with diphtheria toxin or toxoid since, with one exception, non-immune subjects who failed to respond to vaccination did not present a history of diphtheria vaccination. The one non-immune, non-responding subject reporting previous diphtheria vaccination may have provided an erroneous vaccination history. The 'failure' rate is of similar magnitude to that reported for similar combination vaccines (Ruben, Nagel & Fireman, 1978; McCloskey, 1969; Sheffield, Ironside & Abbott, 1978).

No statistically significant differences were observed in the clinical reactivity of the vaccines under test. However, there were several differences, both as regards the incidence and nature of the local reactions observed. Adult-type Td Vaccine caused a slightly higher incidence of local reactions as monitored both by subjective assessment and by inspection of the injection sites. This difference may merely be due to variation in production techniques. Alternatively, it might be attributable to the higher antigen load contained in the Adult-type Td vaccine (White *et al.* 1973) or to the administration of diphtheria toxoid to a partially immune population (Pappenheimer *et al.* 1950). In the latter respect, it should be noted that there was no detectable increase in the incidence of local reactions for 'diphtheria positive', 'tetanus negative', as compared to 'diphtheria negative', 'tetanus negative' recipients. Although fewer local reactions were experienced by recipients of Adsorbed Tetanus Vaccine, the number of subjects reporting pain was approximately double that in the Adult-type Td Vaccine group. Also the pain lasted, on average, for 1 day longer. The increased incidence of pain could not be attributed to a higher aluminium content in Adsorbed Tetanus Vaccine (Collier, Polakoff & Mortimer, 1979) since the concentration of aluminium in the two vaccines was almost identical. It is more likely that the use of Alhydrogel as compared to aluminium phosphate increased the occurrence of pain. Alhydrogel is known to be a more clinically reactive adjuvant for diphtheria toxoid (Holt & Bousfield, 1949), although anecdotally reported to be of equivalent reactogenicity for tetanus vaccines (David & Zehntner, 1971).

It is of interest to note that the overall frequency of both systemic and local reactions was higher than that reported in other trials of similar preparations. This

was not an artefact attributable to a variation in the methods used to record reactions. The difference was still evident when the same parameters were measured. For instance, the incidence of erythema was manyfold greater (i.e. 41 %) in the group receiving tetanus vaccine than that reported for recipients of booster doses of an identical formulation at British Leyland (White, 1980). The local reactions reported were more comparable in terms of incidence and severity to those recorded by Collier *et al.* (1979) following the administration of Adsorbed Tetanus Vaccine 5Lf.

In conclusion, therefore, it appears that a single dose of Adult-type Td Vaccine boosts immunity in the majority of the adult population without being more clinically reactive than Adsorbed Tetanus Vaccine. This might have a useful application in occupational health immunization programmes. However, in the absence of comparative data, it is not possible to assess whether the equivalent reactivity would be maintained if the vaccine were used on a routine basis for prophylaxis against tetanus. Also, it is unclear whether repeated administration of widely spaced doses of low diphtheria toxoid vaccine would eventually raise protective antibody levels in previously unprimed subjects. Such aspects obviously require further investigation.

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