Epidemiol. Infect. (2001), **127**, 451–460. © 2001 Cambridge University Press
DOI: 10.1017/S095026880100629X Printed in the United Kingdom

Immunogenicity and reactogenicity of the adult tetanus–diphtheria vaccine. How many doses are necessary?

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(*Accepted 25 July 2001*)

SUMMARY

The immunogenicity and reactogenicity of the tetanus–diphtheria adult type vaccine was compared in two groups: group I ($n = 201$, 18–30 years old, presumably vaccinated with the DTP vaccine) and group II ($n = 147$, $\geqslant 45$ years old, without vaccination antecedents). Before vaccination, the seroprotection levels for tetanus were 90·5% (group I) and 30·6% (group II). These rose to 99·5% and 81·7%, respectively, after administration of one vaccine dose. For diphtheria, prevaccination seroprotection levels were 38·3% (group I) and 19·0% (group II). These rose to 85·8% and 65·7%, respectively, after vaccination. The logistic regression analysis showed an association between antibody titre and age. In group II, 3 doses of Td vaccine were needed to reach titres similar to those achieved in group I with a single dose. Stated reactogenicity was greater in: young subjects, women, those with higher titres of tetanus antibodies and those receiving other vaccines simultaneously. These results confirm the need for vaccination schedules adapted to the characteristics of each population age-group.

INTRODUCTION

Throughout history, there have been various secular cycles of diphtheria, from the so-called "garrotillo" in Spain at the end of the 16th century to the outbreaks during 1990–8 in Russia, the Ukraine and other countries of the former USSR [1, 2] in which 157000 cases and 4000 deaths were officially reported, mainly in adults and adolescents. In developed countries, the disease was almost eliminated at the end of the 1970s thanks to systematic paediatric vaccination. In Spain, severe outbreaks were registered during the Civil War (4000 deaths in 1939) and the immediate post-war period [3]. Systematic paediatric vaccination was made mandatory in 1964 (DTP at age 3, 5, 7 and 18 months and 4–6 years). In 1967, tetanus vaccination of servicemen was introduced, and in 1998, adult tetanus–diphtheria (Td) vaccination. The last two indigenous cases of diphtheria in Spain were recorded in 1986 [4].

The reduction in the circulation of toxigenic strains of *Corynebacterium diphtheriae*, the result of childhood vaccination [5], makes exposure to natural boosters difficult, thus contributing to an increase in susceptibility to diphtheria. At the same time, better conditions of hygiene help to slow down the circulation of the strains responsible for the cutaneous forms of the disease, favouring the appearance of population groups, basically young adults, where the majority do not possess protective antibodies [6–8].

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This has been shown by various recent studies in Italy [8–11], France [12], Spain [13–16], Germany [17, 18] and the United Kingdom [19]. Although the major epidemic in East European countries has been in remission since 1996 [20], more than 7000 cases were reported in 1997 and more than 2500 in 1998 [2]. Various neighbouring countries have reported imported cases [21].

With respect to tetanus, vaccination programmes, together with aseptic measures, have reduced the notified incidence of the disease to less than 0·2 cases per 100000 inhabitants/year in developed countries. In this group of countries, one of the highest rates of incidence is in Spain, where in recent years, around 50 cases are reported annually, most of them in people over 60 years and in males. Sixty-six percent of those affected have never been vaccinated, and 30% are ignorant of their vaccination history [22, 23]. The situation in Spain with respect to tetanus is far from satisfactory. Although there have been few population-based seroepidemiological studies on the prevalence of tetanus antibodies, the available information shows a low level of protection [24].

The high levels of susceptibility to tetanus and diphtheria have two main causes. Firstly, the development of immunity against these diseases, especially in the case of tetanus is fundamentally vaccine-based, as the natural infection does not confer immunity [25]. Secondly, even in many developed countries where levels of vaccination coverage with the DTP vaccine in the infant population are high [26], the absence of periodic revaccination during adulthood means that many people become susceptible to tetanus and diphtheria again, emphasizing the need for vaccination strategies against both diseases in accordance with WHO recommendations [27].

The Td vaccine is indicated in subjects over 7 years, both for primovaccination and revaccination. In Spain this vaccine has been available since 1995 [13]. The aim of this study was to determine the immunogenicity (how many doses are necessary) and the reactogenicity of the Td vaccine, both in subjects assumed to have been vaccinated and in those not previously vaccinated against these diseases.

METHODS

A prospective non-randomized study was carried out in subjects who attended, for whatever reason, the Adult Vaccination Centre (23000 doses of different vaccines administered annually) of a university hospital over a period of almost 3 years (May 1995 to March 1998). The study protocol was approved by the Clinical Research Ethics Committee of the Hospital Clinic, Barcelona, Spain. After written informed consent was obtained, subjects in whom the Td vaccination was indicated (subjects not vaccinated in the 10 preceding years with the Td vaccination or the monovalent anti-tetanus vaccination) and who agreed to participate in the study, were included. The vaccine used was the combined adult tetanus–diphtheria vaccine with a 0·5 ml dose containing 40 IU of tetanus toxoid and 4 IU of diphtheria antitoxin, adsorbed in 1·5 mg of aluminium hydroxide (0·5 mg of AI+++) and 0·01% of thiomersal as preservative (Smith Kline Beecham Biologicals, Risenxart, Belgium). The vaccination was administered by deep intramuscular injection in the deltoid muscle.

Two groups were established. Group I included subjects between 18 and 30 years of age, corresponding to the birth cohorts of 1965–80, that is, subjects presumed to be previously vaccinated with the DTP vaccine (paediatric vaccination became mandatory in Spain in 1964). This group was given a single dose of Td vaccine as a booster dose. In addition, levels of tetanus and diphtheria antibodies were measured immediately after and 1 month after the dose was given. Group II included subjects of 45 years and over corresponding to birth cohorts anterior to 1953 who stated they had not received previous diphtheria or tetanus vaccinations. This group received 3 doses of Td vaccine at 0, 1 and 6 months, which was considered as primovaccination. In addition blood samples were taken at 0, 1, 6 and 7 months in order to determine levels of tetanus and diphtheria antibodies. In both groups and for each dose, the possible simultaneous administration of other vaccinations and their type was investigated.

Other inclusion criteria were good health according to the clinical history and the physical examination given at inclusion and, in the case of fertile women, the expressed intention of not becoming pregnant during the study period. Exclusion criteria were: (1) A history of significant and persistent problems involving the haematologic, hepatic, renal, cardiovascular or respiratory systems. (2) Acute illness at entry into the study. (3) Chronic pharmacological treatment, including any immunosuppressive drug which might interfere with the response to the vaccine and (4) A history of hypersensitivity which could be stimulated by any component of the vaccine.

Antibody levels were determined by enzymoimmunoanalysis (BINDAZYME, Binding-Site for tetanus and VIROTECH, System-Diagnostika for diphtheria), Seroprotection was defined as antibody titres equal or greater than 0·1 IU/ml. When using neutralization techniques, these levels correspond to absolute seroprotection [28]. The correlation between the results obtained with these techniques and those obtained with ELISA would be low for titres $< 0{\cdot}1$ IU/ml, as the ELISA technique could overestimate the result [29, 30].

The reactogenicity of each dose of vaccine (clinical signs and symptoms) was measured by information registered by vaccinated subjects on cards supplied by the researcher. During days 0–3 general symptoms were noted: axillary temperature, severe headache, discomfort, fatigue, nausea and vomiting and others. Fever was considered to a temperature above 38 °C. Local signs recorded were: pain at the injection site, redness and swelling.

General symptoms and local pain were measured according to the following scale: 0 = Absent, 1 = Mild (the adverse reaction did not significantly interfere with normal life), 2 = Moderate (some changes, which were not considered dangerous for the subject), 3 = Severe (significant changes in general state or incapacity, which were considered dangerous to the subject's health).

The statistical analysis was carried out using the SPSS computer programme. The association between antibody levels and the categorical variables (age and gender) and between the number and type of reported adverse reactions and the categorical variables (age, gender, order of dose) was established using the χ^2 test. The association between pre- and postvaccination titres was measured by McNemar's test. A logistical regression analysis was carried out to control the presence of possible confounding factors and included all the variables which could be associated with the factor studied. The presence or absence of tetanus and diphtheria antibodies were used as dependent variables and age and gender, in the case of prevaccination antibody levels, as independent variables. In the reactogenicity analysis, the presence or absence of a local reaction and of a general reaction were considered as dependent variables and age, gender, the number of doses of other vaccines administered simultaneously and the anterior level of tetanus and diphtheria antibodies as independent variables. The adjusted odds ratios and the 95% confidence intervals were calculated.

RESULTS

Three hundred and forty-eight subjects were included in the study: 201 in group I (age $24{\cdot}3 \pm 3{\cdot}3$ years, range 18–30 years, 30·7% males) and 147 in group II (age $55{\cdot}4 \pm 7{\cdot}7$ years, range 45–79 years, 44·4% males). A complete follow-up was possible in 91% (183/201) subjects in group I and in 69·4% (102/147) subjects in group II.

In group I, at the time of administration of the Td dose, a total of 609 doses of other vaccines were administered simultaneously: 152 hepatitis B, 105 hepatitis A, 89 typhoid (87 oral and 2 parenteral), 47 IPV, 12 rabies and 2 meningococcal A–C, resulting in an average of $2{\cdot}0 \pm 1{\cdot}0$ doses for each dose of Td. Only 2·5% of subjects received only the Td vaccine. In group II, the dose of Td was administered simultaneously with the following other vaccines: (a) 166 together with the first dose of Td: 105 typhoid (100 oral and 5 parenteral), 40 IPV, 8 hepatitis B, 4 meningococcal A–C, 3 influenza and 2 each of rabies, hepatitis A and pneumococcal, with an average of $1{\cdot}1 \pm 0{\cdot}8$ doses for each dose of Td. 20·5% of cases received only Td vaccine. (b) 14 together with the second dose of Td: 9 hepatitis B, 2 rabies and 1 each of oral typhoid, IPV and hepatitis A; an average of $0{\cdot}1 \pm 0{\cdot}3$ doses; 90·8% of subjects received only Td vaccine. (c) 10 together with the third dose of Td: 6 hepatitis B, 2 influenza and 1 each of IPV and hepatitis A, an average of $0{\cdot}1 \pm 0{\cdot}3$ doses for each dose of Td, with 93·8% of subjects receiving only the Td vaccine.

Prevalence of seroprotection before and after vaccination. Immunogenicity

Tetanus

Table 1 shows the seroprotection prevalence for tetanus (titres $\geqslant 0{\cdot}1$ IU/ml) in the pre-vaccination and post-vaccination tests made for each group. Before vaccination, the prevalence of seroprotection against tetanus in groups I and II was 90·5% (182/201) and 30·6% (45/147) respectively [$\chi^2 = 131{\cdot}85$, $P < 0{\cdot}001$]. In each of the groups the prevalence was slightly higher in males than females, although the differences were not statistically significant. In group I, 1 month after administration of one dose of Td vaccine, seroprotective levels were detected in 99·5% (182/183) subjects [McNemar, $P < 0{\cdot}0001$ with respect to pre-vaccination rates] with

Table 1. *Prevalence of seroprotection against tetanus and diphtheria before and after vaccination according to age group and gender*

	Group I		Group II			
Determination (No. studied)	Prev* (201)	Postv* (183)	Prev* (147)	Postv1* (137)	Postv6* (119)	Postv7* (102)
Tetanus						
$\geqslant$ 0·1 IU/ml	90·5†	99·5	30·6	81·7	83·9	99·02
Males	91·8 (56/61)	100 (55/55)	32·3 (21/65)	77·9 (46/59)	78 (39/50)	97·6 (41/42)
Females	90 (126/140)	99·2 (127/128)	29·3 (24/82)	84·6 (66/78)	86·9 (60/69)	100 (60/60)
Diphtheria						
$\geqslant$ 0·1 IU/ml	38·3	85·8	19·04	65·7	65·5	90·2
Males	40·9 (25/61)	89·1 (49/55)	16·04 (11/65)	62·7 (37/59)	60 (30/50)	95·2 (40/42)
Females	37·1 (52/140)	84·4 (108/128)	20·7 (17/82)	67·9 (53/78)	69·6 (48/69)	88·3 (53/60)

* Prev, prevaccination; Postvl, Postv6, Postv7, postvaccination, 1, 6 and 7 months after the first dose.
† Values are percentages with numbers in parentheses.

Table 2. *Determinants of protection against tetanus* (*prevaccination titre*). *Logistic regression analysis*

IU/ml	Independent variables	Adjusted odds ratio (95% CI)	*P*
$\geqslant$ 0·1	Age, years		
	> 54	1·00	
	18–23	30·20 (12·05–75·73)	< 0·00001
	24–30	17·91 (7·81–41·05)	< 0·00001
	45–54	1·04 (0·51–2·13)	n.s.†
	Gender		
	Female*	1·00	
	Male	1·23 (0·68–2·23)	n.s.†

* Reference group.
† n.s., not significant.

no differences between males and females. In group II, the proportion of seroprotected subjects 1, 6 and 7 months after the beginning of the 3-dose schedule was 81·7% (112/137) [McNemar, $P < 0{\cdot}0001$ with respect to prevaccination rates], 83·9% (99/l 19) [McNemar, $P < 0{\cdot}0001$ with respect to prevaccination rates] and 99·0% (101/102) [McNemar, $P < 0{\cdot}0001$ with respect to prevaccination rates] respectively. In all three tests the results were slightly better for females.

At the end of each vaccination series, similar rates of seroprotection were found in both groups (99·5% in group I *vs.* 99% in group II).

The logistical regression analysis (Table 2) of the prevaccination situation confirmed the greater proportion of seroprotected subjects ($\geqslant$ 0·1 IU/ml) in the younger age groups, being markedly greater in the 18–23 and 24–30 years age groups with respect to the > 54 years age group. The 45–54 years age group showed a similar proportion of seroprotected to that of the > 54 years age group.

Diphtheria

Table 1 also shows the prevalences of seroprotection for diphtheria (titres $\geqslant$ 0·1 IU/ml) before and after the vaccination schedule in each of the groups.

Before vaccination, the prevalence of seroprotection against diphtheria in groups I and II was 38·3% (77/201) and 19% (28/147) [$\chi^2 = 14{\cdot}05$, $P < 0{\cdot}0001$], respectively. In group I, as with tetanus, the prevalence of antibodies was slightly greater in males, whereas the reverse was true in group II, although the

Table 3. *Determinants of protection against diphtheria* (*prevaccination titre*). *Logistic regression analysis*

IU/ml	Independent variables	Adjusted odds ratio (95% CI)	*P*
⩾ 0·1	Age, years		
	> 54*	1·00	
	18–23	1·51 (0·76–3·01)	n.s.†
	24–30	1·59 (0·80–3·16)	n.s.
	45–54	0·34 (0·14–0·80)	< 0·01
	Gender		
	Female*	1·00	
	Male	0·99 (0·60–1·66)	n.s.

* Reference group.
† n.s., not significant.

differences were not statistically significant. In group I, 1 month after administration of a dose of Td vaccine, 85·8% (157/183) of subjects had seroprotective levels of antibodies [McNemar, $P < 0{\cdot}0001$, with respect to prevaccination levels], the levels being slightly higher in males. In group II, the levels of seroprotection 1, 6 and 7 months after the beginning of the 3-dose vaccination schedule were 65·7% (90/137) [McNemar, $P < 0{\cdot}0001$, with respect to prevaccination levels) 65·5% (78/119) [McNemar, $P < 0{\cdot}0001$, with respect to prevaccination levels] and 90·2% (92/102) [McNemar, $P < 0{\cdot}0001$, with respect to prevaccination levels], respectively, with a slightly better final result in male subjects (not statistically significant).

At the end of each vaccination series, similar levels of seroprotection were found in both groups (85·8% in group I *vs*. 90·2% in group II).

In the logistical regression analysis (Table 3) of the prevaccination situation, the lowest level of seroprotection (⩾ 0·1 IU/ml) corresponded to the 45–54 years age group and the highest to the younger age groups (reference group > 54 years).

At the end of each vaccination series, similar levels of seroprotection were found in the two groups (95·6% in group I *vs*. 98·03% in group II).

Reactogenicity of the Td vaccine

Local reactions

The adverse local reactions which followed the administration of each dose of vaccine are shown in Table 4. Local reactogenicity in group I was almost twice that of group II. After administration of the first dose, the proportion of subjects reporting ⩾ 1 local reactions was 83·3% (155/186) in group I (booster dose) and 47·5% (66/139) in group II [$\chi^2 = 45{\cdot}36$, $P < 0{\cdot}00000$l]. Within group II, the differences in local reactogenicity related with each dose of vaccine were minimal, oscillating between 40% (second dose) and 47·5% (first dose).

In both age groups and for each dose, females reported a higher number of adverse local reactions, a finding that was statistically significant in all cases except for the third dose in group II.

Table 4 shows the number of local reactions (between 1 and 4) in each group and for each dose. Table 5 shows the type of reaction.

The logistical regression analysis shown in Table 6 confirms the progressively greater reactogenicity of the Td vaccine in the younger age groups (adjusted OR = 7·03, 95% CI 2·76–17·89) in subjects aged 18–23 years with respect to the reference group (> 54 years) and in females (adjusted OR in males = 0·3, 95% CI 0·17–0·53) when the prevaccination titres of tetanus antibodies are included in the model (adjusted OR = 1·6, 95% CI 1·14–2·23). The prevaccination presence of diphtheria antibodies and the simultaneous administration of other vaccines were not associated with greater local reactogenicity in the logistical regression analysis.

General reactions

The general adverse reactions presumably related to each dose of vaccine are shown in Table 4. As with local reactogenicity, general reactogenicity in group I was twice that of group II. In group I, for the first (booster) dose, 40·9% (76/186) subjects reported ⩾ 1 general reactions against 21·6% (30/139) after the first dose in group II [$\chi^2 = 12{\cdot}59$, $P < 0{\cdot}00000$l]. With respect to the general reactogenicity related to each dose of vaccine, the differences were small, oscillating between 17·5% (second dose) and 21·6% (first dose).

Table 4. *Reactogenicity: number of reported adverse reactions*

	Group I	Group II		
Related doses	1st dose (No. = 201)	1st dose (No. = 147)	2nd dose (No. = 137)	3rd dose (No. = 119)
Valid cases	186	139	120	104
Local reactions*	83·3 (155/186)	47·5 (66/139)	40·0 (48/120)	46·1 (48/104)
One	70·9 (110/155)	75·7 (50/66)	50·0 (14/48)	39·6 (19/48)
Two	20·6 (32/155)	10·6 (7/66)	29·2 (14/48)	29·2 (14/48)
Three	8·4 (13/155)	13·6 (9/66)	20·8 (10/48)	29·2 (14/48)
Four	—	—	—	2·1 (1/48)
In males	70·2 (40/57)	31·4 (19/61)	27·4 (14/51)	41·9 (18/43)
In females	89·1 (115/129)	60·2 (47/78)	49·3 (34/69)	49·2 (30/61)
(*P* value)	$P < 0{\cdot}002$	$P < 0{\cdot}001$	$P < 0{\cdot}003$	n.s.†
General reactions*	40·9 (76/186)	21·6 (30/139)	17·5 (21/120)	20·2 (21/104)
One	65·8 (50/76)	63·3 (19/30)	61·9 (13/21)	52·4 (11/21)
Two	25·0 (19/76)	33·3 (10/30)	23·8 (5/21)	33·3 (7/21)
Three	7·9 (6/76)	3·3 (1/30)	14·3 (3/21)	9·5 (2/21)
Four	1·3 (1/76)	—	—	4·8 (1/21)
In males	35·1 (20/57)	16·4 (10/61)	13·7 (7/51)	13·9 (6/43)
In females	43·4 (56/129)	38·5 (30/78)	20·3 (14/69)	24·6 (15/61)
(*P* value)	n.s.	n.s.	n.s.	n.s.

Values are percentages with numbers in parentheses.
* Subjects with one or more reactions.
† n.s., not significant.

Table 5. *Reactogenicity: types of adverse reactions reported*

	Group I	Group II		
Related doses	1st dose (No. = 201)	1st dose (No. = 147)	2nd dose (No. = 137)	3rd dose (No. = 119)
Local reactions	(213)	(91)	(82)	(93)
Pain*	71·8 (153)	75·8 (69)	61·0 (50)	45·2 (42)
Redness	10·3 (22)	8·8 (8)	24·4 (20)	29·0 (27)
Swelling	18·3 (38)	15·4 (14)	14·6 (12)	25·8 (24)
General reactions	(110)	(42)	(32)	(35)
Fever	3·6 (4)	0 (0)	0 (0)	2·8 (1)
Discomfort†	35·5 (39)	30·9 (13)	31·3 (10)	20·0 (7)
Headache‡	43·6 (48)	54·8 (23)	50·0 (16)	45·7 (16)
Nausea/vomiting§	7·3 (8)	4·8 (2)	12·5 (4)	14·3 (5)
Other**	10·0 (11)	9·5 (4)	6·2 (2)	17·1 (6)

Values are percentages with numbers in parentheses.
* In group I: 74% mild and 26% moderate. In group II (3 doses): 78% mild and 22% moderate.
† In group I: 75% mild and 25% moderate. In group II (3 doses): 68% mild and 32% moderate.
‡ In group I: 79% mild and 21% moderate. In group II (3 doses): 79% mild and 21% moderate.
§ In group I: 100% mild. In group II (3 doses): 64% mild and 36% moderate.
** In group I: 73% mild and 27% moderate. In group II (3 doses): 67% mild and 33% moderate.

Females reported greater general reactogenicity, but the differences were not statistically significant in any case.

Table 4 also shows the number of general reactions (between 1 and 4) in each group and for each dose. Table 5 shows the type of reactions, the most frequent being discomfort and severe headache.

The logistical regression analysis in Table 6 confirms the greater general reactogenicity of the Td vaccine observed in the younger age groups. In the

Table 6. *Reactogenicity to the first dose of Td vaccine. Logistic regression analysis*

	Variable (reference group)	Adjusted odds ratio (95% CI)	*P*
Local reactions	Age (> 54 years)		
	18–23	7·03 (2·76–17·89)	< 0·00001
	24–30	4·22 (1·63–10·96)	< 0·003
	45–54	2·44 (1·15–5·19)	< 0·02
	Gender (female)		
	Male	0·30 (0·17–0·53)	< 0·00001
	Other vaccines (0 doses)	1·01 (0·74–1·36)	n.s.*
	AntiTET titre† (< 0·1 IU/ml)	2·54 (1·31–4·93)	< 0·006
	AntiDIP titre‡ (< 0·1 IU/ml)	1·42 (0·74–2·73)	n.s.
General reactions	Age (> 54 years)		
	18–23	3·15 (1·21–8·18)	< 0·02
	24–30	2·47 (0·90–6·78)	n.s.*
	45–54	2·47 (0·99–6·17)	< 0·0535
	Gender (female)		
	Male	0·58 (0·33–1·00)	< 0·0511
	Other vaccines (0 doses)	1·43 (1·10–1·84)	< 0·007
	AntiTET titre† (< 0·1 IU/ml)	1·22 (0·62–2·40)	n.s.
	AntiDIP titre‡ (< 0·1 IU/ml)	1·15 (0·67–1·97)	n.s.

* n.s., not significant.
† AntiTET, prevaccination antitetanus antibodies.
‡ AntiDIP, prevaccination antidiphtheria antibodies.

model, gender (adjusted OR in males = 0·58, 95% CI 0·33–1·0) and the simultaneous administration of other vaccines (adjusted OR = 1·43, 95% CI 1·10–1·84) are significantly related. Neither the prevaccination presence of tetanus or diphtheria antibodies are associated in the logistical regression analysis with the appearance of general adverse reactions.

DISCUSSION

Seroprotection before and after vaccination

Tetanus

The results of this study confirm a low level of protection against tetanus in the adult population which can be explained both by the history of low vaccination coverage in infancy in the older age groups and by the absence of periodic revaccinations [18, 22, 23]. In younger subjects such as the 18–30 years age group, the proportion of seroprotected subjects reaches 90% even though they claim not to have received a booster dose within the last 10 years. The administration of a single dose of Td vaccine gives protection to almost all subjects vaccinated [31].

Almost a third of subjects $\geqslant 45$ years who denied being vaccinated previously possessed tetanus antibodies. Given that such a situation without previous vaccination can be considered exceptional, the probability of recall bias must be considered, meaning that it is likely that some of these subjects have in fact received tetanus vaccinations in the past. In any case, more than one dose of vaccine (three) is required to reach seroprotection levels comparable to those of the 18–30 years age group [32], thereby guaranteeing protection against a disease in which there is no herd immunity.

In each age group, the minimal differences between genders both before vaccination and during the vaccination period is a recommendation for the use of the same vaccination strategies for both sexes. The simultaneous administration of other vaccines does not influence the formation of tetanus antibodies [33].

Diphtheria

As previously remarked, the lack of exposure to natural (reduced circulation of toxigenic strains of *Corynebacterium diphtheriae*) and artificial (lack of periodic revaccination) boosters explains the low levels of protection against diphtheria reported in various European countries [7, 8, 12, 16, 18, 19]. Leaving to one side differences in the type of population studied, in laboratory tests, in threshold protection levels (absolute or partial) and other methodological differences, the results of our study

are consistent with these studies and also show the need to use vaccination schedules which are differentiated with respect to age, the fundamental paradigm of antecedents of diphtheria vaccination. We know that adults in general have an imprecise idea of their vaccination history, usually because there is no documented history or because of the span of time or inadequate conservation of documents [34]. For this reason it is vital, in addition to encouraging the use of individual immunization registers, to develop group strategies in consonance with the situation of each sector of the population. The results of this study may provide useful information in this respect.

The present study also confirms the utility of the Td vaccine in conferring protection against tetanus and diphtheria [13]. In the younger population groups, presumably vaccinated in infancy (the history of the introduction of the vaccine and the levels of coverage reached in each country are determining factors in this respect), a single dose of the vaccine will normally be sufficient [31, 35]. A recent study by Nicolay et al. [31] carried out in Germany, Austria and Slovenia and limited to the younger population, reaches similar conclusions. Specific situations such as an imminent trip to endemic or epidemic areas [36] might require additional individualized doses of vaccine. In subjects with a negative or uncertain vaccination history it seems advisable to carry out a 3-dose schedule, as this ensures levels of protection of almost 100% against both tetanus and diphtheria. Although the absolute protection levels in the case of diphtheria are somewhat lower (90%), they are sufficient to ensure herd immunity [27].

The logistical regression analysis confirms that the initial vaccination immune situation is primarily age-dependent [37], presumably because the possibility of previous primovaccination is more certain and closer in time. Neither gender nor the simultaneous administration of other vaccines play a relevant role in the response to the diphtheria vaccine. Some studies have found lower levels of diphtheria antibodies in females [15, 17, 19, 38] which they have taken to indicate a poor response to the vaccination in females [17]. In some countries, but not in Spain, lower levels of diphtheria antibodies in females might be related to Td vaccination of male servicemen. Despite the fact that the dose of Td was administered at the same time as one or more other vaccines, the seroresponse rates to a booster dose of Td led to a very high seroresponse rate to tetanus and a relatively high seroresponse rate to diphtheria. This lack of interference by other vaccines is in accordance with the current recommendations on the simultaneous administration of vaccines [33] and is also consistent with current trends towards the use of combined vaccines in both children and adults.

Safety of the Td vaccine

In daily clinical practise we are often faced with the need to administer various vaccines simultaneously, underlining the importance of carrying out naturalistic studies of the type postulated by Lasagna [39] in 1974. Unlike clinical trials, these studies attempt to evaluate the product (in this case a vaccine) in real or 'natural' conditions of use, both for the doctor and the subject. This may affect the immunogenicity of each vaccine and, of course, the safety profile. In the present study, only 2·5% of the younger age group and a progressively greater proportion (20·5%, 90·8% and 93·85% in doses 1, 2 and 3 respectively) of the $\geqslant$ 45 years age group received only the Td vaccine, a fair reflection of the way vaccines are usually administered in a Vaccination Centre.

The reactogenicity of the tetanus and diphtheria toxoids is related to numerous factors [13, 40–46] such as: the formula of the vaccine, previous levels of antitoxin, the route of administration, the adjuvants used, the age of the subjects and, of course, the methods used to measure adverse effects. Although this makes comparisons difficult, the results of our study are broadly consistent with other studies [40, 46]. The greater local reactogenicity (83% in the 18–30 years age group and between 40% and 47% according to the order of the dose in the $\geqslant$ 45 years age group) and general reactogenicity (41% in the 18–30 years age group and 17–21% in the $\geqslant$ 45 years age group) are clearly associated with age, and this is presumably related to the greater number of previous vaccinations in the younger age group. The logistic model confirms the progressive increase of reactogenicity at a younger age as well as the influence of the prevaccination titre of tetanus antibodies which leads to a two-and-a-half fold increase in the number of adverse local reactions. Curiously, women suffer greater local reactogenicity than males, both in the raw and logistic analyses.

The most common local adverse event was pain at the site of inoculation, while the general reactions included discomfort and headache. In all cases, the reactions were of light or moderate intensity. As might be expected, the general reactions were more common

in subjects who received simultaneous doses of other vaccines (hepatitis B, hepatitis A, typhoid, etc.). Younger subjects and females reported a slightly higher amount of general symptoms, but this was not influenced by anterior levels of either tetanus or diphtheria antitoxin. The lower frequency of general symptoms (5–10%) found in other studies [13, 41–43] is probably due to the isolated use of the Td without the hypothetical synergetic effect of other immunizations.

In conclusion, in subjects presumably not vaccinated in the past, a complete cycle of three doses is needed to reach a level of adequate protection against both tetanus and diphtheria. In subjects presumably vaccinated in infancy in whom $\geqslant 10$ years have passed since the last dose, one dose of Td vaccine is sufficient to achieve protective titres against both diseases. The use of additional doses would increase the reactogenicity without providing any additional advantage. A Task Force on Adult Immunization [34] has recommended a single booster at age 50 years for persons who have completed the full paediatric series, including teenage and young adult boosters. This schedule would be an equivalent alternative strategy to the traditional recommendation of Td boosters every 10 years. The present study was not designed to show how long protection lasts [47], but provides additional evidence indicative of long-term protection in subjects who have presumably completed a primary immunization series with tetanus and diphtheria toxoids.

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