

Adverse reactions to the preschool (fifth) dose of adsorbed diphtheria-pertussis-tetanus vaccine in Canadian children

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Objective: To quantify accurately the rate of adverse reactions after the preschool (fifth) dose of adsorbed diphtheria toxoid-pertussis vaccine-tetanus toxoid (DPT) vaccine and to test the hypothesis that large local reactions are attributable to the diphtheria toxoid.

Design: Double-blind randomized controlled trial.

Setting: Suburban community public health unit.

Participants: Healthy children 4 to 5 years of age with a history of having received four doses of adsorbed DPT vaccine.

Interventions: Subjects were given either the standard DPT vaccine (with 25 Lf units of diphtheria toxoid) or a modified DPT vaccine (with 10 Lf units of diphtheria toxoid). They were assessed 24 hours later by a nurse. Serum samples obtained before vaccination were tested for diphtheria and tetanus antitoxin levels by means of neutralization assay and enzyme-linked immunosorbent assay.

Main outcome measures: Rates of large local reactions (an area of redness or swelling or both of 5 cm or greater) 24 hours after vaccination in the two groups. Relation between serum antitoxin levels before vaccination and the rate of large local reactions in each group.

Results: Of the 250 subjects enrolled 124 received the standard vaccine and 126 the modified one. Large local reactions occurred in 71% of the subjects receiving the standard vaccine and 52% of those receiving the modified one ($p < 0.01$). In the former group large erythematous reactions occurred significantly more often in those with an elevated prevaccination diphtheria antitoxin level than in those without an elevated level; no relation was found between such reactions and the prevaccination tetanus antitoxin level. Reduced arm movement was evident in 45% of the children in the two groups. Few had systemic adverse reactions.

Conclusions: Large local reactions occur frequently after the preschool administration of the DPT vaccine. These reactions are uncomfortable but not serious. They result in part from the large amount of diphtheria toxoid in the standard DPT vaccine.

Objectif : Quantifier avec précision le taux de réactions indésirables après l'administration en âge préscolaire d'une dose (la cinquième) de vaccin adsorbé renfermant l'anatoxine diphtérique, le vaccin coquelucheux et l'anatoxine tétanique (DCT) et

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vérifier l'hypothèse selon laquelle des réactions locales importantes sont attribuables à l'anatoxine diphtérique.

Conception : Essai contrôlé, randomisé et à double insu.

Contexte : Service de santé publique communautaire de banlieue.

Participants : Enfants en bon état de santé, âgés de 4 à 5 ans et ayant reçu quatre doses de vaccin DCT adsorbé.

Interventions : Les sujets ont reçu le vaccin DCT standard (avec 25 unités Lf d'anatoxine diphtérique) ou un vaccin DCT modifié (avec 10 unités Lf d'anatoxine diphtérique). Les enfants ont été évalués par une infirmière 24 heures plus tard. Les échantillons de sérum prélevés avant la vaccination ont fait l'objet de tests pour déterminer les taux d'antitoxine diphtérique et tétanique au moyen d'un dosage par neutralisation ou par titrage avec immuno-absorbant lié à une enzyme, soit la méthode ELISA.

Principales mesures de résultats : Taux de réactions locales importantes (une surface rougie ou enflée ou les deux de 5 cm ou plus) 24 heures après la vaccination dans les deux groupes. Relation entre les taux d'antitoxine sérique avant la vaccination et le taux de réactions locales importantes dans chaque groupe.

Résultats : Parmi les 250 sujets inscrits, 124 ont reçu le vaccin standard et 126 le vaccin modifié. Des réactions locales importantes sont survenues chez 71 % des sujets ayant reçu le vaccin standard et 52 % de ceux qui ont reçu le vaccin modifié ($p < 0,01$). Dans le premier groupe, des réactions érythémateuses importantes sont survenues beaucoup plus souvent chez les sujets dont le taux d'antitoxine diphtérique était élevé avant la vaccination que chez ceux dont le taux n'était pas élevé; on a constaté aucune relation entre de telles réactions et le taux d'antitoxine tétanique avant la vaccination. Une réduction du mouvement des bras était évidente chez 45 % des enfants dans les deux groupes. Les réactions générales indésirables étaient rares.

Conclusions : Des réactions locales importantes surviennent fréquemment après l'administration en âge préscolaire du vaccin DCT. Ces réactions sont inconfortables, mais elles ne sont pas graves. Elles sont en partie attribuables à la quantité importante d'anatoxine diphtérique dans le vaccin DCT standard.

Recent reports¹⁻³ have suggested that Canadian children experience large local reactions to the preschool (fifth) dose of diphtheria toxoid-pertussis vaccine-tetanus toxoid (DPT) vaccine more often now. In Alberta, a province with extensive surveillance of adverse reactions within a public health vaccine delivery system, the number of such reactions after the fourth (at age 18 months) or fifth (at 4 to 6 years) dose of DPT vaccine increased from 25 in 1984 to 484 in 1986.¹ In 1987 a survey in Alberta involving 669 children receiving either the fourth or the fifth dose indicated that 11% had an area of local redness or swelling of 5 cm or more in diameter.¹ In British Columbia the administration of DPT vaccine to 202 kindergarten students in Cranbrook in 1988 resulted in large local reactions in 26%, redness or swelling of the entire upper arm occurring in 4%.² Over 15% of vaccinated students missed school allegedly because of adverse reactions.

In a prospective study involving 111 children followed up through a routine schedule of DPT vaccination, an area of redness or swelling 5 cm or greater in diameter was reported at the injection site after 2.7% of the third doses were given (at 6 months of age), 14% of the fourth doses (at 18 months) and 20% of the fifth doses (at 4 to 5 years).³ Local reactions occurred significantly more often after a booster shot than after a primary dose ($p < 0.001$).

Cody and collaborators⁴ studied the occurrence of local reactions after US-formulation DTP vaccines were administered to children as a booster or a primary dose. They found that among 876 children receiving the fifth dose minor local complaints occurred frequently (redness in 45%, pain in 74%), but large local reactions (5 cm or greater in diameter) were infrequent (occurring in less than 5%) (Dr. James Cherry: personal communication, 1990).

Large local reactions after the fourth and fifth doses of DPT vaccine are a new problem in Canada that emerged after the change to adsorbed products in the early 1980s. Adsorbed DPT vaccine prepared by Connaught Laboratories Limited, Willowdale, Ont., has been shown to be less reactogenic than its fluid counterpart in infants given a single dose and has compared favourably with an adsorbed vaccine produced in the United States.⁵ However, with repeated doses the superior immunogenic effects of the adsorbed vaccine may result in higher-than-intended antibody response rates among some children, predisposing them to local Arthus-type reactions after a booster dose.⁶ The Canadian program differs from most others: five doses of an adsorbed vaccine with a high diphtheria toxoid content (25 Lf units per dose) are given. A similar vaccine is used in Britain but is routinely given only four times; the US program involves five doses, but the vaccine has a

lower diphtheria toxoid content (6.7 to 12.5 Lf units per dose).

This study was undertaken to quantify accurately the nature and rate of adverse reactions (evaluated by nurses rather than by parents) to the fifth dose of DPT vaccine. Our second objective was to test the hypothesis that large local reactions result mainly from the diphtheria toxoid component of the standard vaccine. Two approaches were used: (a) a double-blind randomized controlled study of local reactions to the standard vaccine and a modified vaccine with a reduced diphtheria toxoid content and (b) an analysis of the relations between serum antitoxin levels before vaccination and subsequent local reaction rates.

Methods

Patient selection

The study was approved by the Ethics Committee of the University of British Columbia, Vancouver. Healthy children 4 to 5 years of age needing a preschool dose of DPT vaccine were recruited from the clientele of the Boundary (public) Health Unit, Surrey, BC; written informed consent was obtained from a parent. The health unit vaccinates about 40% of the children in this suburban middle-class area. The selection criteria were as follows: receipt of four doses of adsorbed DPT vaccine as infants, no contraindications to a booster dose, no immunocompromising condition and no fever or evidence of poor health on the day of vaccination.

To achieve random allocation each child was assigned a unique code number in sequence upon entry into the study and given the vaccine from a vial labelled with the corresponding code number. Treatment was assigned on the basis of lists of random numbers, generated in balanced blocks of 40.

Vaccination

The vaccines were dispensed in identical single-dose (0.5-mL) vials bearing only the patient's code number. Each dose of standard vaccine, prepared by Connaught Laboratories, was drawn from one licensed lot (no. 3722-21) and contained 25 Lf units of diphtheria toxoid, 5 Lf units of tetanus toxoid, 4 to 12 protective units of whole-cell pertussis vaccine, 1.5 mg of aluminum phosphate and 0.01% thimerosal. Each dose of the modified vaccine, specially prepared by Connaught Laboratories for this study, contained 10 Lf units of diphtheria toxoid, the amounts of the other constituents being similar to those in the standard vaccine.

The vaccines were derived from different manu-

facturing lots. The preparations looked identical. The vials were stored and transported at 2°C to 8°C; freezing was avoided. The vaccine was injected into the deltoid muscle by skilled nurses using 25-gauge needles 22 mm in length. Oral poliovirus vaccine was given at the same visit to most subjects. Parents were not counselled to use acetaminophen prophylactically because this is not routine for this age group, but they were free to give it therapeutically.

Just before the injection a fingerprick blood sample was taken from each child. The serum was obtained promptly and stored at -20°C or -70°C before testing. Aliquots were tested for diphtheria antitoxin by means of microneutralization assay at Connaught Laboratories or enzyme-linked immunosorbent assay (ELISA) at the Vaccine Evaluation Center, Vancouver, and for tetanus antitoxin by means of ELISA at Connaught Laboratories. The samples were labelled with the subject's code number and tested in a blinded fashion in both laboratories. The ELISA used to determine the diphtheria antitoxin level had previously been standardized against the microneutralization assay; the results were expressed as antibody units (AU) per millilitre.

Measurement of adverse reactions

Parents were advised of the possibility of local and systemic adverse effects after vaccination but were not asked to make a special effort to detect or record such effects. Children were visited at home by one of six trained study nurses approximately 24 hours after vaccination. First the available caregivers were asked to report any adverse effects and to rate the severity of each symptom; the details were recorded by the nurse. Use of medications or physician contact was noted. The nurse then assessed the child, measuring oral temperature, noting general appearance and activity level, and examining the injected arm for redness, swelling, tenderness and limitation of motion. Redness and swelling were measured with a clear, flexible ruler. Tenderness was graded as mild (pain with pressure on injection site), moderate (pain with light touch) or severe (guarding of area). The nurse assessed limitation of motion by asking the child to make hair-combing motions with each arm and comparing the movements. The nurses were previously instructed in assessment techniques, but interrater reliability was not determined.

Statistical analysis

The data were analysed at the Vaccine Evaluation Center. Additional quality assurance measures were applied, such as the use of a detailed instruction manual by the study nurses, content checking of all reports and integrity checks of half of

all the coded data entered into the database.

Statistical analyses were performed using the Number Cruncher (J.L. Hintze, Kaysville, Utah) and SAS/STAT (SAS Institute Inc., Cary, NC) software programs. Contingency tables were constructed to compare demographic, serologic and adverse reaction data between and within the two study groups; Fisher's exact test or χ^2 tests with continuity adjustment were used for such comparisons. A one-sided Fisher's test was used to compare local adverse reaction rates between the groups, because the reaction rate in the group receiving the modified vaccine was expected to differ in only one direction (fewer reactions). Student's *t*-test was used to compare age distributions between the two groups. Linear regression analysis was used to compare diphtheria antitoxin levels obtained through the neutralization assay and ELISA.

Results

Of the 250 children enrolled 124 received the standard vaccine and 126 the modified one. The two groups were similar in terms of age, sex, ethnic origin and serum antitoxin levels before immunization (Table 1). Comparable proportions of children in each group participated as infants in other vaccine studies not involving experimental DPT vaccines. A written record of four previous doses of adsorbed DPT vaccine was available for over 92% of the subjects, although all enrollees were said by parents to have had four "baby shots." The left arm was

used for injection more often than the right (85% v. 15%), depending on the subject's preference.

Adverse reactions

The follow-up visit was made 1 day after vaccination in every instance. The mother gave the history in most cases (Table 2); other informants were the father, the grandparents and a babysitter. Two subjects in each group were considered to have intercurrent illness on the basis of the appearance overnight of coryza, sore throat or coughing. About three-quarters of the children in each group complained of soreness of the injected arm, but only 10 (8%) complained of feeling sick. No child was sick enough to cause the parent to contact a physician.

At the follow-up visit only 14 (6%) of the children looked ill to the nurses. Only one child in each group was febrile (temperature greater than 38°C). Ten (8%) in each group had marked reduction in arm movement, although minor limitation was evident in 45%. Tenderness at the injection site was present in 69% of the subjects, the rate being similar in the two groups. Ten children (8%) in each group had moderate to severe tenderness.

The nurses' observations regarding redness and swelling at the injection site are summarized in Table 3. The simple rates of these reactions (regardless of their size) did not differ significantly between the two groups. In the standard vaccine group areas of redness or swelling or both of 5 cm or greater and of 7.5 cm or greater occurred in 71% and 31% of the

Table 1: Characteristics of 250 children before receipt of a standard or modified preschool dose of diphtheria toxoid-pertussis vaccine-tetanus toxoid (DPT) vaccine

Characteristic	Vaccine; no. (and %) of children	
	Standard (n = 124)	Modified (n = 126)
Mean age (and standard deviation [SD]), mo	57.8 (4.9)	58.8 (4.5)
Sex		
Male	64 (52)	68 (54)
Female	60 (48)	58 (46)
White race	121 (98)	125 (99)
Written record of four previous doses of DPT vaccine	115 (93)	116 (92)
Participation in previous vaccine study	78 (63)	87 (69)
Receipt of vaccine in left arm	105 (85)	107 (85)
Concurrent receipt of oral poliovirus vaccine	112 (90)	113 (90)
Serum diphtheria antitoxin level before vaccination, IU/mL	(n = 115)	(n = 116)
≤ 0.32	56 (49)	52 (45)
≥ 0.64	59 (51)	64 (55)
Serum tetanus antitoxin level before vaccination, IU/mL	(n = 122)	(n = 123)
≤ 0.20	64 (52)	75 (61)
≥ 0.21	58 (48)	48 (39)

children respectively, whereas the corresponding rates in the modified vaccine group were 52% ($p < 0.01$) and 18% ($p < 0.04$). The point estimate of the difference in the rates of reactions of 7.5 cm in diameter or greater was 12.4% (95% confidence limits 1.8% and 22.9%).

The parents were aware of only a few of the local reactions documented by the nurses. In the standard vaccine group only 4 of the 53 instances of redness of 3 cm in diameter or greater were reported to the nurse before her examination, even though the parents had been specifically questioned about local reactions. Similarly, the parents detected only 32 of 52 instances of decreased arm motion. Equally limited awareness existed among the parents of children given the modified vaccine. However, the parents were not asked to do anything special to detect local reactions. Only 45% of all the children with local reactions of 7.5 cm or more in size were considered by their parents to have had a moderate or severe reaction.

Antitoxin levels

Blood samples collected before vaccination were sufficient in volume for measuring the serum diphtheria antitoxin level (by means of neutralization assay) in 231 children (92%) and the serum tetanus antitoxin level in 245 (98%); 50 samples (from standard vaccine recipients only) were available for

detecting the diphtheria antitoxin level through ELISA.

Four (2%) of the subjects had a serum diphtheria antitoxin level (as detected by means of neutralization assay) below the minimum protective level of 0.01 IU/mL; for 108 (47%) the level was 0.32 IU/mL or less, and for 217 (94%) it was 2.56 IU/mL or less. The diphtheria neutralization assay and ELISA results correlated ($r = +0.69$), but the ELISA values were on average 8.8 times higher throughout the range of values.

Three subjects (1%) had a serum tetanus antitoxin level below the minimum protective level of 0.01 IU/mL; for 140 (57%) the level was 0.20 IU/mL or less, and for 230 (94%) it was 0.60 IU/mL or less.

In total, 13 children (6%) were inadequately or marginally protected (having an antitoxin level of 0.01 IU/mL or less) against tetanus or diphtheria or both (in two instances). The distribution of the antitoxin levels did not differ between the two groups.

In the standard vaccine group children with a serum diphtheria antitoxin level of 0.64 IU/mL or more were more likely than those with a level of 0.32 IU/mL or less to experience an area of redness 7.5 cm or more in diameter ($p = 0.009$) and were uniquely at risk for reactions 10 cm or more in diameter (Table 4). A relation was also apparent between the diphtheria antitoxin level determined through ELISA and the frequency of large areas of redness: 93% of the subjects with a level of 6.0 AU/mL or more experienced an area of redness 5 cm or greater in diameter, as compared with only 48% of those with a lower level ($p = 0.003$).

No association was evident between the diphtheria antitoxin levels and local swelling. For example, an area of swelling 7.5 cm or more in diameter was evident in 10 (18%) of 56 subjects with an antitoxin level of 0.32 IU/mL or less and in 19 (32%) of 59 subjects with a level of 0.64 IU/mL or more; this difference was not significant.

Among the 21 recipients of the standard vaccine who had a very low serum diphtheria antitoxin level

Table 2: Events reported by parent* or child within 24 hours after vaccination

Event	Vaccine; no. (and %) of children	
	Standard	Modified
Any adverse effect	95 (77)	103 (82)
Soreness at injection site	91 (73)	97 (77)
Sick feeling	10 (8)	10 (8)
Intercurrent illness	2 (2)	2 (2)

*The mother provided the history for 112 (90%) of the children receiving the standard vaccine and for 112 (89%) receiving the modified one.

Table 3: Local reactions observed by the study nurses 24 hours after vaccination

Diameter of reaction, cm	Reaction; no. (and %) of children			
	Redness		Swelling	
	Standard vaccine	Modified vaccine	Standard vaccine	Modified vaccine
No reaction	66 (53)	74 (59)	33 (27)	38 (30)
≤ 2.4	3 (2)	13 (10)	4 (3)	5 (4)
2.5-4.9	11 (9)	11 (9)	11 (9)	21 (17)
5.0-7.4	24 (19)	21 (17)	47 (38)	42 (33)
7.5-9.9	13 (10)	5 (4)	22 (18)	14 (11)
≥ 10	7 (6)	2 (2)	7 (6)	6 (5)

(0.08 IU/mL or less) local reactions occurred at an appreciable rate: 24% had an area of redness 5 cm or greater in diameter and 33% an area of swelling 7.5 cm or greater in diameter. These children also had a relatively low diphtheria antitoxin level determined through ELISA (less than 7.0 AU/mL).

No association was found between the serum tetanus antitoxin level and local reactions. For example, among 64 children with a level of less than 0.2 IU/mL 11% had an area of redness 7.5 cm or greater in diameter and 19% an area of swelling of the same size; the corresponding rates among 58 children with an antitoxin level of 0.2 IU/mL or more were 22% and 29% respectively. These differences were not significant.

In the modified vaccine group no relation was evident between local reactions and prevaccination diphtheria or tetanus antitoxin levels. For instance, among 52 children with a serum diphtheria antitoxin level of 0.32 IU/mL or less 29 (56%) had an area of redness 5 cm or greater in diameter and 13 (25%) an area of swelling of the same size. Among 64 whose level was 0.64 IU/mL or more the same degree of redness and swelling occurred in 28 (44%) and 12 (19%) respectively.

Discussion

Although large local reactions occurred frequently after the preschool dose of the standard DPT vaccine few of the children complained of feeling sick after vaccination or showed signs of systemic adverse effects. None required medical attention. Many complained of arm soreness and local tenderness, and nearly half had reduced arm movement. A total of 55 (44%) of those in the standard vaccine group and 58 (46%) in the modified vaccine group were given one or more doses of analgesic medication.

The rates of a reaction 5 cm or greater in diameter 24 hours after vaccination were higher than any reported previously in Canada;^{1,2} however, there were important differences in the definitions, such as the duration of reactions (2 to 3 days in previous studies). Our study provided only a "snapshot" of reactions at 24 hours, precluding the use of earlier definitions. The use of nurse evaluators may have accounted for our high rates of swelling, which parents tended to underestimate. When only simple rates of pain, redness and swelling are considered, regardless of the severity, our results are comparable to those reported by Cody and collaborators⁴ for the fifth dose of the US formulation: pain 74% and 75% respectively, redness 45% and 47%, and swelling 45% and 73%. However, few US children experience local reactions of the severity observed in this study. When our data are projected to the 400 000 preschool children vaccinated annually in Canada we can estimate that 32 000 will have arm soreness to the point of near immobility the next day.

Large areas of redness or swelling or both developed less often after injection of the modified vaccine, although the simple rates of pain, redness and swelling were the same in the two groups. The magnitude of the reduction in the rate of large reactions (42% fewer instances of redness or swelling 7.5 cm or more in diameter) seems to be attributable to the smaller content of diphtheria toxoid rather than the variation in reactogenic effects of pertussis-containing vaccine lots, which is usually minor.⁷ However, the vaccines used in our study contained different manufacturing lots of whole-cell pertussis vaccine and may have differed in reactogenic effects. The endotoxin content of the lots was not determined.

The low serum antitoxin levels before vaccination supported the appropriateness of the timing of the second booster dose. Thirteen children (6%) were

Table 4: Relation between serum diphtheria antitoxin levels before vaccination and occurrence of local redness after receipt of standard DPT vaccine

Assay; antitoxin level	Diameter of red area, cm; no. (and %) of samples		
	≥ 5 cm	≥ 7.5 cm	≥ 10 cm
Neutralization assay, IU/mL			
≤ 0.32 (n = 56)	15 (27)	3 (5)	0
≥ 0.64 (n = 59)	26 (44)	13 (22)	6 (10)
p value*	NS	0.009	0.027
Enzyme-linked immunosorbent assay (ELISA), AU/mL			
< 6.0 (n = 35†)	17 (48)	5 (14)	1 (3)
≥ 6.0 (n = 15†)	14 (93)	10 (67)	5 (33)
p value*	0.003	0.0005	0.007

*Determined by means of two-tailed Fisher's exact test; NS = not significant.

†Fewer samples were available for the ELISA.

unprotected or marginally protected (having antibody levels of 0.01 IU/mL or less) against diphtheria (six children), tetanus (seven) or both (two). Of interest, low serum diphtheria antitoxin levels (0.08 IU/mL or less) did not protect the subjects from reactions to the vaccine: 24% had an area of redness 5 cm or greater in diameter and 71% an area of swelling of the same size. All six children who had a serum diphtheria antitoxin level below the minimum protective level had an area of redness or swelling 5 cm or greater in diameter; the two who were also unprotected against tetanus had an area of swelling more than 7.5 cm in diameter after vaccination.

The fact that large local reactions occurred more frequently in the subjects with an elevated diphtheria but not an elevated tetanus antitoxin level provides additional evidence of a major role of diphtheria toxoid in these reactions. Similar associations have been reported among adolescents whose rates of local reaction after receiving tetanus toxoid^{8,9} or diphtheria toxoid¹⁰ were higher among those with an elevated antitoxin level before vaccination. It is paradoxical that reactions should be a problem in children with relatively low diphtheria antitoxin levels. Prevacination levels may be less relevant than the speed with which secondary antibody responses occur, since the latter was a better predictor of local reactions in one study of adults given tetanus toxoid boosters.¹¹ Alternatively, the gold standard neutralization assay would underestimate the total diphtheria antibody level if non-neutralizing antibodies were present. The consistently higher diphtheria antitoxin levels measured by means of ELISA in our study and another¹² raise this possibility. Diphtheria toxin is a large molecule (62 000 daltons) with many antigenic sites.¹³ Alterations in its molecular structure due to formalin exposure may create additional epitopes on the toxoid molecules; responses to non-native or non-neutralizing epitopes may be greater with repeated doses of alum-adsorbed toxoid. Exploration of the immunobiologic features of booster responses¹³ to various diphtheria toxoid preparations seems warranted.

The reactogenic effects of the modified vaccine assessed suggest that the reduced diphtheria toxoid content is still too high for a booster dose. Alternatively, other vaccine constituents such as aluminum phosphate and whole-cell pertussis vaccine may be contributing to the local reaction rate. Cody and collaborators⁴ found that omission of pertussis vaccine from primary vaccination decreased the occurrence of local redness and tenderness almost five-fold. The role of pertussis vaccine in local reactions to booster doses has not been determined. The modified vaccine used in this study was intended only as a probe for diphtheria-related reactogenic

effects and is not improved sufficiently to warrant studies of its safety and immunogenic effects for primary vaccination. The specific contribution of each vaccine constituent to the local reaction rate among preschool children should be assessed for the development of a rational strategy for reformulating the DPT vaccine given to Canadian children.

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