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Reduced-Antigen Combined Diphtheria-Tetanus-Acellular Pertussis Vaccine (Boostrix™)

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Contents

Abstract

▲ The reduced-antigen combined diphtheria-tetanus--acellular pertussis vaccine (dTpa) is intended for use as a booster dose in individuals aged ≥4 years.

▲ A single dose of dTpa elicited generally similar levels of antibodies against pertussis antigens (pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]) as a similar monovalent pertussis booster vaccine (ap) in adolescents or adults, irrespective of their prevaccination serological status or vaccination history.

▲ Levels of antibodies directed against diphtheria toxoid were similar in recipients of dTpa or a licensed reduced-antigen combined diphtheria-tetanus booster vaccine (Td). However, levels of antitetanus antibodies were significantly higher in recipients of Td vaccines compared with those receiving dTpa.

▲ Similar serological response rates were observed for anti-PT, -FHA and -PRN between those receiving dTpa or ap and a similar high percentage of recipients of dTpa and the Td vaccines had seroprotective levels of antibodies against diphtheria and tetanus toxoid.

▲ The most frequently reported local adverse reactions following immunisation with dTpa included pain, redness and swelling; general symptoms included fatigue, headache and fever.

Features and properties of the reduced-antigen combined diphtheria-tetanus-acellular pertussis booster vaccine (dTpa; Boostrix™)	
Indication	
Booster vaccination against diphtheria, tetanus and pertussis for children (aged ≥4 years), adolescents and adults	
Mechanism of action	
Vaccine	
Vaccine components	
≥2 International Units (IU; 2.5 limits of flocculation [Lf]) diphtheria toxoid, ≥20IU (5Lf) tetanus toxoid, 8μg pertussis toxoid, 8μg filamentous haemagglutinin and 2.5μg pertactin	
Dosage and administration	
Dose	0.5mL
Route of administration	Intramuscular injection (deltoid)
Frequency of administration	One dose every 10 years
Adverse events	
Most common	Local (pain, redness and swelling at the injection site) and general (fatigue, headache and fever)

Pertussis, or whooping cough, is a highly contagious respiratory illness caused by the Gram-negative bacterium *Bordetella pertussis*.[1] Widespread childhood immunisation against pertussis has been effective in decreasing the incidence of pertussis, but has not eliminated it.[2,3] It is estimated that annually there are approximately 45 million cases of pertussis worldwide, resulting in 400 000 deaths each year.[4]

Surveillance data indicate that the incidence of pertussis in adolescents and adults is increasing.[3,5,6] In the US, despite a childhood vaccination programme, the annual incidence rate of pertussis reported to the Centers for Disease Control and Prevention during 1997–2000 was 2.7 per 100 000 individuals and 49% of patients were aged 10 years or older.[3] This indicates that immunity to pertussis, from vaccination or infection, is not lifelong.[5,7] Although the disease is usually mild in older patients, of primary concern is the possibility that these patients may transmit pertussis to unvaccinated or incompletely vaccinated infants at risk of severe complications or death.[1,6-9]

In many countries worldwide, adolescents and adults receive booster vaccinations with a reduced-antigen combined diphtheria-tetanus booster vaccine (Td) at 10-year intervals to maintain immunity to diphtheria and tetanus.[10,11] To combine an acellular pertussis booster vaccine with this already widely used Td vaccine may be advantageous.

A reduced-antigen, combined diphtheria-tetanus-acellular pertussis booster vaccine (dTpa; Boostrix™[1]) has been developed as a booster vaccination against diphtheria, tetanus and pertussis for individuals aged 4 years and older.[12] The dTpa vaccine contains five antigens:

- a minimum of 2 International Units (IU) diphtheria toxoid (2.5 limits of flocculation [Lf])
- a minimum of 20IU tetanus toxoid (5Lf)
- 8μg pertussis toxoid (PT)
- 8μg filamentous haemagglutinin (FHA)
- 2.5μg pertactin (PRN).[12]

The quantities of the pertussis antigens in dTpa are approximately one-third of the levels found in the well established primary paediatric combined diphtheria-tetanus-acellular pertussis vaccine (DTPa; Infanrix™).[12]

In this review, data on the immunogenicity and reactogenicity (i.e. tolerability) of a single booster dose of the dTpa vaccine in adolescents (aged 10–13 years) and adults are presented. The review focuses on comparative data.

1. Immunogenicity

The immunogenicity of the dTpa vaccine 1 month after vaccination has been compared with that of a similar monovalent, three-component (8μg PT, 8μg FHA and 2.5μg PRN) acellular pertussis vaccine (ap) and three licensed Td vaccines in three fully published, randomised, single-blind clinical studies. One study was conducted in Finland and included healthy adolescents (aged 10–13 years; n = 510) and adults (aged 18–73 years; n = 847) who had received primary immunisation with four doses of combined diphtheria-tetanus and whole-cell pertussis at 3, 4, 5 and 24 months of age[13]. The other two studies (conducted in Belgium[14] and Australia[15]) included healthy adults (aged 18–73 years; n = 847); the vaccination history of adults was not reported.

Prior to vaccination the majority of adolescents and adults were seropositive for antibodies to tetanus toxoid (≥0.1 IU/mL; 85–95%), diphtheria toxoid (≥0.016 IU/mL; 73–97%) and pertussis antigens PT, FHA and PRN (≥5 ELISA U/mL; 54–73.1%, 97–98.2% and 70–74.5%, respectively).[13-15] There was no significant difference between groups in the percentages of seropositive subjects or in geometric mean concentrations (GMC) for any of the antibodies before vaccination.

Healthy individuals generally received a single 0.5mL dose of dTpa vaccine, or a 0.5mL dose of the ap vaccine and/or a 0.5mL dose of a licensed Td vaccine.[13-15] In the Belgian study, patients were randomised to receive a single dose of either the

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

dTpa, ap or Td vaccine.[14] In the other two studies, recipients of the Td or ap vaccine received the alternative vaccine 1 month later.[13,15] The composition of the Td vaccines used in the studies varied slightly. In the Finnish study, the Td vaccine (Lederject®) contained 2Lf of diphtheria toxoid and 5Lf of tetanus toxoid,[13] whereas the Td vaccine in the Belgian study (Tedivax pro Adulto®) contained ≥1.5Lf of diphtheria toxoid and ≥10Lf of tetanus toxoid.[14] In the Australian study the Td vaccine (ADT®) contained ≥2IU (2Lf) of diphtheria toxoid and ≥20IU (6Lf) of tetanus toxoid.[15] All vaccinations were given by deep intramuscular injection into the deltoid region.[13-15]

The antitetanus antibody response 4 and 10 days after vaccination with dTpa has also been compared with a licensed tetanus vaccine (Tetavax®) in a randomised, single-blind clinical trial in 320 healthy adults.[16] The tetanus vaccine contained ≥40 IU/mL tetanus toxoid and is indicated for tetanus postexposure prophylaxis in patients with recent injuries that might be contaminated with tetanus spores.[17] Details regarding the dosage and route of administration for each of the vaccines used in this trial were not reported in the abstract.

Exclusion criteria in trials generally included a history of diphtheria or tetanus; a diphtheria or tetanus vaccination or exposure to pertussis within the past 5 years; a known history of nonresponse or any serious adverse reaction to a previous diphtheria, tetanus or pertussis vaccination; the administration of blood products or immunoglobulins up to 3 months prior to the trial or the administration of any vaccine 3 months before the trial.[13-15] Patients with a history of allergic reaction likely to be exacerbated by any component of the vaccine or any underlying condition likely to affect the response to immunisation and pregnant or lactating women were also excluded.[13-15]

Trials reported the percentage of participants with seroprotective levels of antidiphtheria[13-15] and antitetanus[13-16] antibodies. Antidiphtheria and antitetanus antibody titres of 0.01 IU/mL are generally accepted to be protective against diphtheria[18] and tetanus.[19] As no correlation between antibody levels and protection against pertussis has yet been identified, and no protective efficacy data are available for acellular pertussis vaccines in adolescents and adults, trials reported the serological response rates to pertussis antigens (defined as the appearance of antibodies [≥5 EU/mL] in initially seronegative participants [seroconversion] or at least a 2-fold increase of a positive prevaccination level in initially seropositive participants).[13-15]

The study in adolescents[13] also included a proliferation assay of peripheral blood mononuclear cells (PBMC) in order to measure the cell-mediated immune (CMI) response to pertussis antigens. A positive CMI response was defined as antigen-induced proliferation at least 4-fold higher than spontaneous proliferation (stimulation index ≥4).[13]

Response to Pertussis Antigens

- Postvaccination GMCs of antibodies against PT, FHA and PRN were similar in adolescent recipients of dTpa or ap 1 month after vaccination (figure 1).[13] Similarly, in the larger of the two adult studies (n = 548), anti-PT, -FHA and -PRN levels were similar 1 month after vaccination with dTpa or ap (figure 1).[15] However, in the smaller of the adult studies (n = 299), the anti-PT GMC was significantly higher in the ap vaccine group than in those receiving dTpa (125 vs 76 EU/mL; $p < 0.05$).[14]
- In the trials in which it was reported, all adolescent and nearly all adult vaccinees demonstrated a serological response (as defined above) against at least one of the pertussis antigens 1 month after vaccination.[13,14] Similar serological response rates were observed between those receiving dTpa and ap (anti-PT 92% and 93.7% vs 96% and 96.7%, anti-FHA 96.8% and 97% vs 98% and 98.9%, and anti-PRN 97.9% and 99% vs 97.8% and 100%, respectively).[13,14]
- The longer term immunogenicity of the vaccines in adults was assessed in a subgroup analysis 12 months after vaccination in one study (n = 98).[15] The rate of decrease in GMCs of antibodies against each of the pertussis antigens over 12 months was similar between those vaccinated with dTpa or ap, and antibody levels in both vaccine groups were

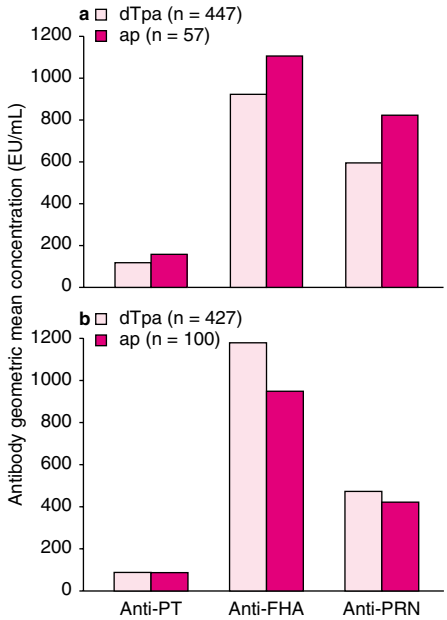

Fig. 1. Efficacy of the reduced-antigen combined diphtheria-tetanus-acellular pertussis vaccine (dTpa) and a similar pertussis vaccine (ap) against pertussis antigens. Antibody levels against pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) in (**a**) adolescents aged 10–13 years (baseline concentrations of anti-PT 10 and 8 EU/mL, anti-FHA 58 and 53 EU/mL and anti-PRN 11 and 10 EU/mL for dTpa and ap recipients, respectively)[13] and (**b**) adults (baseline concentrations of anti-PT 9 and 7.8 EU/mL, anti-FHA 41 and 34 EU/mL and anti-PRN 11 and 10 EU/mL for those receiving dTpa and ap, respectively)[15] 1 month after immunisation with dTpa (≥2IU [2.5 limits of flocculation {Lf}] diphtheria toxoid, ≥20IU [5Lf] tetanus toxoid, 8μg PT, 8μg FHA and 2.5μg PRN) or ap (8μg PT, 8μg FHA and 2.5μg PRN) in two single-blind, randomised trials.

higher at the 12 month follow-up than before booster vaccination.[15] Twelve months after vaccination with dTpa, GMCs of anti-PT, -FHA and -PRN were 30, 374 and 207 EU/mL, respectively, compared with 24, 328 and 142 EU/mL, respectively, with ap.[15]

- In the large adult study, there were also no significant differences in the percentage of adult participants who were seropositive for pertussis antibodies between those receiving the dTpa vaccine or the ap vaccine at 1 month (99–100% vs 97–100%) and 12 months (98–100% vs 90–100%) after immunisation.[15]
- The CMI response to the pertussis antigens was similar following immunisation with either dTpa or ap in adolescents.[13] After immunisation with dTpa or ap, large increases in the geometic mean value of proliferation of PBMCs in response to each of the pertussis antigens were observed (8- to 10-fold vs 16- to 18-fold).[13] The percentage of patients with a positive CMI response rate (stimulation index ≥4) in response to PT, FHA or PRN were similar following vaccination with dTpa and ap (98% vs 100%, 96% vs 100% and 88% vs 100%, respectively).[13]

Response to Diphtheria and Tetanus Antigens

- Both dTpa and Td were highly immunogenic for the diphtheria and tetanus toxoids in adolescents.[13] GMCs of antidiphtheria toxoid antibodies in adolescents were similar following vaccination with dTpa or Td; however, GMCs of antitetanus toxoid antibodies in adolescents were significantly higher after vaccination with Td than after dTpa ($p < 0.001$) [figure 2].[13] Nonetheless, the authors thought this difference was unlikely to be of any clinical significance because all participants had antitetanus toxoid antibody levels higher than those considered to be protective against tetanus.[13]
- The two studies in adults also showed no difference in postvaccination antidiphtheria GMCs 1 month after vaccination with dTpa or Td (1.6 and 1.7 vs 2.0 and 2.1 IU/mL).[14,15] However, similar to those of adolescents, antitetanus GMCs were significantly higher following vaccination with Td than with dTpa (11.8 and 13.0 vs 8.1 and 9.9 IU/mL; $p < 0.05$) in both studies in adults.[14,15]
- Nonetheless, the dTpa vaccine had similar efficacy to the Td vaccines in terms of the proportions of adolescent or adult participants with seroprotective levels of antibodies against diphtheria and tetanus toxoids.[13-15] One month after vaccination, a similar percentage of adolescent and adult recipients of dTpa and Td had antidiphtheria (88.4–100% vs 90.1–100%) and antitetanus (99.8–100% vs 98.9–100%) antibody levels of at least 0.1 IU/mL.[13-15]

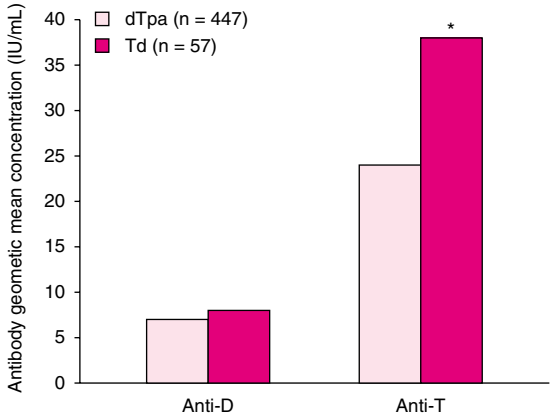

Fig. 2. Relative immunogenicity of two vaccines against diphtheria and tetanus antigens in adolescents. Geometric mean concentrations of antidiphtheria (anti-D) and antitetanus (anti-T) antibodies 1 month after immunisation with the reduced-antigen combined diphtheria-tetanus-acellular pertussis vaccine (dTpa; ≥2IU [2.5 limits of flocculation {Lf}] diphtheria toxoid, ≥20 [5Lf] tetanus toxoid, 8μg pertussis toxoid, 8μg filamentous haemagglutinin and 2.5μg pertactin) or a licensed diphtheria-tetanus vaccine (Td; 2Lf diphtheria toxoid, 5Lf tetanus toxoid) in adolescents aged 10–13 years in a single-blind, randomised trial. Baseline concentrations were 0.2 IU/mL for diphtheria and 0.5 IU/mL for tetanus for both groups. * $p < 0.001$ vs dTpa.[13]

- Additionally, in a separate study a similar percentage of participants receiving dTpa or Td were seroprotected against tetanus (≥0.1 IU/mL) 10 days after vaccination (90.1% vs 92.2%).[16]
- In a subgroup analysis (n = 98) 12 months after the booster injection, GMCs of antidiphtheria (0.4 vs 0.7 IU/mL) and antitetanus (1.9 vs 3.4 IU/mL) antibodies were similar in those vaccinated with dTpa or Td and remained higher than prevaccination levels in both vaccine groups (2–2.4 times the prevaccination level and 3.5–5 times the prevaccination level).[15] A high rate of seropositivity was also observed for antidiphtheria and antitetanus antibodies 12 months after vaccination with dTpa or Td (figure 3).[15]

2. Tolerability

In all trials, participants or their guardians recorded the incidence of specified local reactions and general adverse events for 14 days after each vaccination.[13-15] The incidence of unsolicited adverse events was also recorded for a period up to 30 days after vaccination. Tolerability data from the largest trial in adults (n = 548) are shown in figure 4.

Local Reactions

- Pain at the injection site was the adverse event most frequently reported by participants or guardians after vaccination with dTpa (73–88.5% of participants), Td (82.7–85% of participants) or ap (56–71.9% of participants).[13-15]
- Other frequently reported local symptoms in adolescents and adults vaccinated with dTpa, Td or ap were redness (32–33.3% vs 34.7–53.3% and

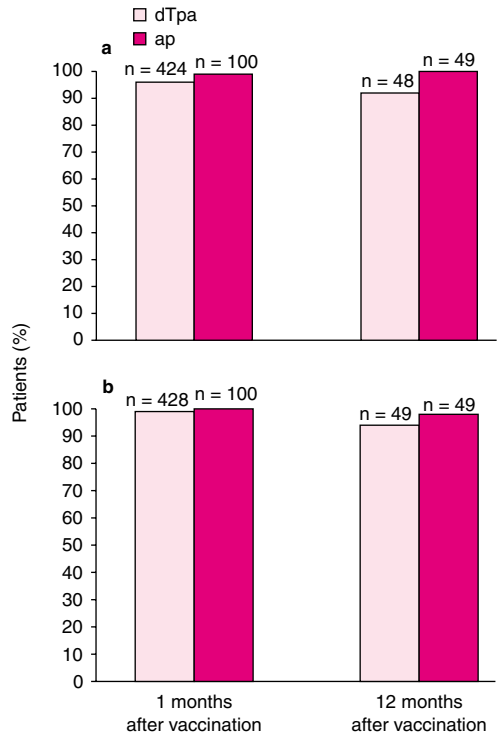

Fig. 3. Seropositivity for antidiphtheria and antitetanus antibodies in adults receiving reduced-antigen combined diphtheria-tetanus-acellular pertussis (dTpa) or a licensed diphtheria-tetanus (Td) vaccine. The percentage of adult patients who were seropositive for antibodies directed against (**a**) diphtheria toxoid (anti-D; titres ≥0.016 IU/mL) and (**b**) tetanus toxoid (anti-T; titres ≥0.1 IU/mL) at 1 and 12 months after immunisation with dTpa (≥2IU [2.5 limits of flocculation {Lf}] diphtheria toxoid, ≥20IU [5Lf] tetanus toxoid, 8μg pertussis toxoid, 8μg filamentous haemagglutinin and 2.5μg pertactin) or Td (≥2IU [2Lf] diphtheria toxoid and ≥20IU [6Lf] tetanus toxoid) vaccines in a single-blind, randomised trial.[15] **ap** = pertussis vaccine.

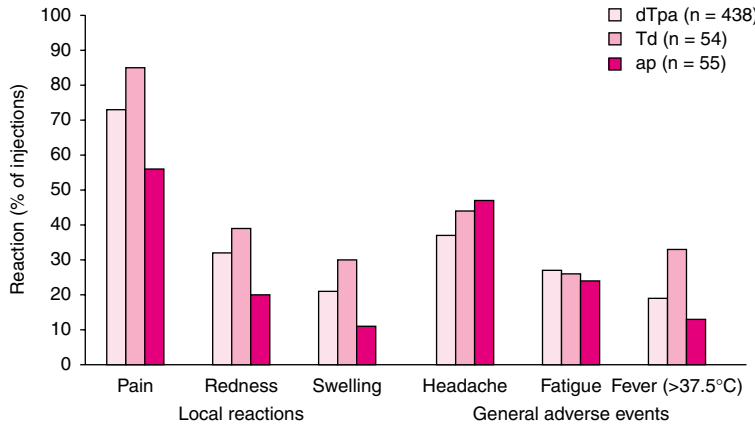

Fig. 4. Tolerability of a combined trivalent diphtheria-tetanus-acellular pertussis booster vaccine (dTpa), a licensed diphtheria-tetanus vaccine (Td) and a pertussis vaccine (ap) in adults. Incidence of the most common local reactions and general adverse events per dose in adults randomised to receive dTpa (≥2IU [2.5 limits of flocculation {Lf}] diphtheria toxoid, ≥20 [5Lf] tetanus toxoid, 8μg pertussis toxoid [PT], 8μg filamentous haemagglutinin [FHA], 2.5μg pertactin [PRN]) or Td (≥2IU [2Lf] diphtheria toxoid, ≥20IU [6Lf] tetanus toxoid) and ap (8μg PT, 8μg FHA, 2.5μg PRN) administered 1 month apart. The number of local and general adverse events up to 14 days after vaccination was recorded by participants.[15]

8.5–20%, of participants respectively) and swelling (21–35.0% vs 26.5–46.7% of participants and 10.4–15.3% of participants, respectively).[13-15]

- The incidence of pain, redness and swelling was similar for adult participants receiving dTpa or Td.[14,15] There was no significant difference in the incidence of pain and swelling in adolescents receiving dTpa or Td; however, the incidence of redness was significantly lower after vaccination with dTpa than with Td in adolescents (33.0% vs 53.3% of participants; $p < 0.001$).[13]
- The majority of local symptoms were mild and transitory and all adverse events that were considered probably or possibly related to the vaccine resolved without major medical intervention or sequelae.[13-15]

General Adverse Events

- The incidence of general adverse events was similar across all vaccine groups.[13-15] The most frequently reported general adverse event by participants or guardians after administration of dTpa, Td or ap was fatigue (27–56.2% vs 26–50% and 24–40.7% of participants).[13-15]
- Other general adverse events frequently reported by dTpa, Td or ap recipients were headache (32.3–51.3% vs 33.7–51.7% and 33.3– 47% of participants) and fever (≥37.5°C) [5.2–19% vs 8.3–33% and 4.2–13% of participants].[13-15]
- General symptoms of clinical significance were generally low after vaccination with dTpa (0–15%) and occurred at a similar incidence after vaccination with Td (0–22%) or ap (0–18%).[13-15]
- One study reported that only half of the general adverse events were considered probably or possibly related to vaccination.[14] While another study reported there was no significant difference between the vaccine groups for the incidence of unsolicited general adverse events.[15]
- The incidence of late onset reactions (including local reactions and general adverse events occurring ≥3 days after immunisation) was reported as low and similar for the three vaccine groups.[13-15] For example, in the study in adolescents the incidence of late onset reactions was 14.5%, 8.3% and 6.7% for the dTpa, Td and ap vaccine groups, respectively.[13] In the largest study, fever was the most common late onset reaction in participants receiving dTpa, Td or ap (10%, 15% or 7% of participants).[15]

3. Dosage and Administration

A single 0.5mL dose of dTpa via a deep intramuscular injection is indicated for booster vaccination against diphtheria, tetanus and pertussis for individuals aged 4 years and older at intervals of generally 10 years.[12]

Individuals who have not completed a primary series of vaccination with diphtheria and tetanus toxoids should not be vaccinated with dTpa.[12]

As with other combined diphtheria-tetanus-acellular pertussis vaccines, vaccination with dTpa is contraindicated if there is a known hypersensitivity to any component of the vaccine or if there is a history of encephalopathy of unknown origin, transient thrombocytopenia or neurological complications within 7 days of a previous administration of a diphtheria, tetanus or pertussis vaccine.[12]

4. Reduced-Antigen Combined Diphtheria-Tetanus-Acellular Pertussis Vaccine: Current Status

The reduced-antigen, combined diphtheria-tetanus-acellular pertussis booster vaccine has been launched in has been launched in a number of European countries, Australia, and some South-American and Asian countries as a booster vaccination against diphtheria, tetanus and pertussis in children (>4 years of age), adolescents and adults.

The reduced-antigen, trivalent booster vaccine provides a similar serological response rate against pertussis antigens as an acellular pertussis vaccine with similar seroprotection against diphtheria and tetanus and similar reactogenicity to licensed reduced-antigen combined diphtheria-tetanus booster vaccines.

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