

Extensive Swelling Reactions Occurring After Booster Doses of Diphtheria-Tetanus-Acellular Pertussis Vaccines

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Extensive local reactions are recognized to occur after administration of the fourth and fifth booster doses of diphtheria-tetanus-acellular pertussis (DTaP) vaccines. The incidence of these reactions is being delineated by prospective studies. Retrospective evaluations suggest that entire proximal limb swelling occurs in 2 to 6 percent of children given booster doses of DTaP vaccines. The reactions subside without sequelae, but they may be misdiagnosed as cellulitis and lead to unnecessary medical intervention. The pathogenesis of these reactions probably is multifactorial. Evidence suggests that both antigen content and prevaccination immunity have roles. Important, unanswered questions are the safety of revaccinating a child who previously has had an extensive local reaction and the safety of introducing further DTaP boosters into the adolescent and adult populations.

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Concerns about reactions to whole cell pertussis-diphtheria toxoid-tetanus toxoid (DTP) vaccines led to the development, licensure, and use of subunit acellular pertussis-diphtheria toxoid-tetanus toxoid vaccines (DTaP). DTaP vaccines are used exclusively now to immunize against pertussis in North America. Studies consistently have shown fewer and less severe systemic reactions after administration of DTaP compared with DTP vaccines.¹⁻³ Postvaccination surveillance of hospital admissions to 10 centers in Canada showed a 75 percent reduction in hypotonic-hyporesponsive episodes after the switch from the routine use of DTP to DTaP.⁴ In the United States, approximately one-third fewer reports of vaccine adverse events after booster doses of DTaP have been filed compared with the DTP era.

Rates of Extensive Swelling Reactions (ESR)

Extensive local reactions have been reported to occur after administration of many different vaccines. However, because studies showed a lower incidence of local reactions after administration of the primary infant series of DTaP compared with DTP,¹ investigators were surprised when

ESR to booster doses first were observed.^{5,6} An increasing rate of and severity of local reactions with successive doses now has been documented in prelicensure evaluations of several different DTaP vaccines.¹⁻³ Swelling of the entire injected arm or thigh was reported with the acellular pertussis vaccine studied in Japan and Sweden in the 1980s.^{7,8} However, the proposed explanation was that vaccine had been given by the subcutaneous route. Researchers now appreciate that aluminum-adjuvant vaccines induce less local reactivity when given intramuscularly. A shorter needle length is associated with increased local reactions, probably because the shorter needle results more frequently in subcutaneous deposition of vaccine.⁹

The National Institutes of Health (NIH) sponsored multicenter, acellular pertussis trials (MAPT) of the safety and immunogenicity of multiple, different DTaP vaccines, compared with 2 whole cell vaccines, gave an opportunity to evaluate limb swelling that occurred after administration of different DTaP manufactured vaccines.¹⁰ Because extensive swelling was not an anticipated reaction, parents were not instructed to observe for it specifically. After the study was completed, the comments sections of the parent's diary cards of postvaccination were reviewed. A total of 1,015 children had been given a fourth consecutive dose of 1 of 12 different DTaP vaccines.² The parents of 2 percent of these children described entire thigh swelling (ETS) noted within 48 hours of administration of the vaccination. The rates and heights of temperatures were no higher in those children with ESR than those without large swelling reactions. Interestingly, parents of 40 percent of the children with ESR said they had no pain whatsoever, and 40 percent were reported to have no erythema at the injection site. Descriptions of a few children did indicate that they had severe

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1045-1870/03/1403-0005\$30.00/0

doi:10.1053/spid.2003.50031

pain. Swelling resolved by day 4 in most children, and no lasting sequelae were shown.¹⁰ ETS has been reported significantly more commonly in children given 4 doses of DTaP, compared with those who received a primary series of DTP followed by a booster dose of DTaP.

A fifth dose of 6 of these same DTaP vaccines was administered to a convenience subset of 121 children in the MAPT study.³ None of these children was noted to have swelling of the entire upper arm. However, 4 (2.7%) of 146 children given a mixed series of 5 DTaP vaccines did have entire upper arm swelling reported by the parents.¹⁰ A prospective evaluation of local reactions occurring after 5 consecutive doses of a DTaP vaccine containing a 2-component acellular pertussis vaccine is being conducted by Group Health Cooperative.¹¹ A preliminary report indicated that large reactions at the injection site are common occurrences after administration of the preschool booster of DTaP. Erythema greater than or equal to 10 cm. in diameter was observed in 5 percent of the 88 children injected in the thigh and in 9 percent of the 201 injected in the arm. At least moderate pain was reported in 38 percent of the children with erythema 10 cm or greater. Interestingly, an apparent association of large reaction with higher body mass index was noted.

Before the NIH MAPT study, ESR had been reported only after administration of DTaP vaccines produced by one manufacturer. An important observation of the NIH trial was that ETS was noted after the fourth dose of 9 of the 12 different DTaP vaccines made by 8 different manufacturers. The MAPT is the only comparative evaluation of local reactions occurring after DTaP vaccination, and the number of children receiving each vaccine was insufficient to compare the rates of ESR among different vaccines. ESR now has been described with all DTaP vaccines licensed. Unfortunately, because reaction data were not collected in a consistent manner in precensure studies, one cannot compare rates reported by different manufacturers.

Pathogenesis

Acellular pertussis vaccines contain different components of *Bordetella pertussis*. All acellular pertussis vaccines contain pertussis toxoid. A 2-component vaccine is made of pertussis toxoid plus filamentous hemagglutinin. Pertactin, a 69 kD outer membrane protein, is added in the 3-component vaccines. The 5-component acellular pertussis vaccine also contains 2 fimbriae. One or more of these pertussis antigens are combined with diphtheria toxoid and tetanus toxoid to constitute the combined DTaP vaccines. The quantities of the various pertussis antigens vary among vaccines, as do the quantities of diphtheria and tetanus toxoids. ESR was observed on the NIH study with DTaP vaccines containing 1, 2, 3, and 5 pertussis components. The relationship between the rates of ETS that occurred after administration of the fourth dose of DTaP and quantities of the vaccine components commonly shared (ie, pertussis toxoid, diphtheria toxoid, tetanus toxoid, aluminum) were explored in the MAPT study. A significant association by

linear regression was found between increasing diphtheria toxoid content (0.02) and a strong trend for the pertussis toxoid component (0.06). However, the same relationships were not observed in children with lesser degrees of swelling (ie, greater than or equal to 5 cm. but less than entire thigh) after receiving dose 4 or dose 5. Also, the association between diphtheria toxoid content and ETS was not seen consistently with every vaccine.¹⁰ Therefore, the relationships between the contents of vaccines and ESR need to be studied in larger numbers of children before firm conclusions can be made.

One hypothesis is that extensive local reactions are Arthus reactions caused by high prevaccination antibody. No difference in the distribution of prevaccination or post-vaccination serum antibody content to pertussis toxoid, diphtheria toxoid, or tetanus toxoid could be shown in the MAPT study. However, the numbers studied were small. A study in German children compared the predose 5 antibody concentrations with the size of the swelling reactions. A significant association was found between prevaccination antibody amount to pertussis toxoid ($P = 0.015$), and trends also were suggested for associations with tetanus toxoid and pertussis toxoid antibody.¹² Thus, some evidence suggests that high levels of IgG antibody before administration of booster have a role in ESR.

The pathophysiology of the range of local reactions seen after administration of booster injections of DTaP vaccine probably is multifactorial and may be a cumulative increased response to several component antigens. Both whole cell pertussis and tetanus toxoid have been documented to cause large local reactions. Aluminum compounds also have been proposed to induce vaccine reactions.⁸ Additionally, serum immunoglobulin G antibodies are only one aspect of the immune response. Previous studies have shown an association between severe local reactions and levels of immunoglobulin E antibody to the toxoid vaccines, which are enhanced by aluminum absorption.¹³⁻¹⁶ Cell-mediated immunity may have a role in sensitization of certain individuals to repeated doses of toxoid vaccines, and this hypothesis needs to be assessed. Some data indicate that children who have large erythematous reactions after receiving DTaP vaccines more commonly react to skin test patches containing diphtheria toxoid or acellular pertussis.¹⁷

Practical Implications

An obvious question raised by the observation of extensive local reactions to DTaP vaccination is whether the toddler and preschool doses are necessary. The incidence of pertussis is increasing in North America, particularly in the adolescent age group. The apparent explanation is waning protection from whole cell DTP.¹⁸⁻²⁰ Thus, elimination of the preschool dose seems unwise. However, the toddler, or fourth, dose of DTaP may not be necessary for protection against pertussis. Follow-up of children given 3 component DTaP vaccines in the Italian efficacy study indicates that children remained protected against pertussis at least up to

age 6 years.²¹ However, studies in Scandinavia indicate that boosters in the second year of life and preschool appear to be needed to sustain protective levels of diphtheria antitoxin.^{22,23}

To date, no data are available on the safety of revaccination of children who have had an extensive local reaction to a prior dose of DTaP. A revaccination study is planning to be conducted in the Clinical Immunization Safety Centers funded by the Centers of Disease Control and Prevention. Until these important data are available, the recommended course is for children to receive all 5 doses of DTaP before entry into school because of the continued widespread circulation of pertussis.

At least 2 vaccine manufacturers are developing a reduced diphtheria and pertussis antigen content vaccine intended for use as booster doses for adolescents and adults. Perhaps these preparations will be safer and adequately immunogenic for use as the fourth and fifth dose. Evaluations of these diphtheria and pertussis antigen content vaccines in adolescents and adults have shown that they are immunogenic, and reactions are acceptable. However, these studies have been conducted in individuals who received previous whole cell DTP. Conducting safety evaluations in populations that have received acellular pertussis-containing vaccines for the entire series of immunizations will be very important.

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