Extensive Swelling After Booster Doses of Acellular Pertussis–Tetanus–Diphtheria Vaccines

Margaret B. Rennels, MD*; Maria A. Deloria, BSc†; Michael E. Pichichero, MD§; Genevieve A. Losonsky, MD*; Janet A. Englund, MD‖; Bruce D. Meade, PhD‡; Edwin L. Anderson, MD**; Mark C. Steinhoff, MD#; and Kathryn M. Edwards, MD‡‡

ABSTRACT. Background. Diphtheria and tetanus toxoid combined with acellular pertussis (DTaP) vaccines are less reactogenic than diphtheria and tetanus toxoid combined with whole cell pertussis (DTwP) vaccines. However, local reactions increase in rate and severity with each successive DTaP dose, and swelling of the entire injected limb has been reported after booster doses.

Methods. We reviewed reports of swelling of the entire thigh or upper arm after the fourth and fifth dose, respectively, of DTaP vaccines administered in the National Institutes of Health multicenter comparative DTaP studies. Relationships were explored among reports of severe swelling, rates of other reactions, quantity of vaccine contents, and prevaccination and postvaccination antibody levels to pertussis toxin, tetanus toxin, and diphtheria toxin.

Results. Entire thigh swelling was an unsolicited reaction reported in 20 (2%) of the 1015 children who received 4 consecutive doses of the same DTaP vaccine. The reaction was associated with 9 of the 12 DTaP vaccines evaluated. Although there were no reports of swelling of the entire upper arm in 121 children given a fifth dose of the same DTaP, 4 (2.7%) of 146 recipients of 5 doses of a mixed schedule of DTaP vaccines experienced such swelling. Rates of other reactions were higher in children with entire thigh swelling than in those without. Of the children with entire thigh swelling, 60% had local pain, and 60% had erythema. All swelling subsided spontaneously without sequelae. There was a significant linear association between the rates of entire thigh swelling after dose 4 and diphtheria toxoid content in the DTaP products. Lesser degrees of swelling (>50 mm but less than entire limb) correlated with pertussis toxoid content after dose 4 and aluminum content after dose 5. No relationship was established between levels of serum antibody to diphtheria, tetanus, or pertussis toxin and rates of swelling of the entire thigh.

Conclusions. Booster doses of DTaP vaccines can cause entire limb swelling, which is usually associated with redness and pain. Our data suggest that this extensive swelling reaction may be more common with vaccines containing high diphtheria toxoid content.

ABBREVIATIONS. DTaP, acellular pertussis combined with tetanus and diphtheria toxoid vaccines; DTwP, whole cell pertussis combined with tetanus and diphtheria toxoid vaccines; PTx, pertussis toxin; DTx, diphtheria toxin; TTx, tetanus toxin; Dtxd, diphtheria toxoid; Txd, tetanus toxoid; CBER, Center for Biologics Evaluation and Research.

A cellular pertussis combined with tetanus and diphtheria toxoid vaccines (DTaP) have consistently been shown to be less reactogenic than whole cell pertussis combined with tetanus and diphtheria toxoid vaccines (DTwP).1–4 Some practitioners and parents therefore may have the impression that DTaP injection is free of side effects. It is now well-established that rates of local reactions increase with each subsequent dose of DTaP vaccine.3–7 Indeed, there have been 2 published reports of swelling of the entire injected thigh after a fourth consecutive dose of 2- and 3-component DTaP vaccines.8,9 We studied the rate at which swelling of the entire injected muscle was spontaneously reported after booster doses of DTaP vaccines and ascertained whether it occurred with different DTaP products. Reaction forms filled out by parents of children participating in the National Institutes of Health-supported multicenter trials of the safety and immunogenicity of fourth and fifth consecutive doses of various DTaP vaccines were reviewed. Associated reactions were evaluated to examine whether swelling of the entire muscle was a benign reactive edema, as had been reported previously,9 or whether associated symptoms were present. Additionally, to explore whether there was a relationship between severe swelling and the quantity of a particular component in the involved vaccines, rates of entire limb swelling and swelling >50 mm (excluding those with whole limb swelling) were correlated with the content of selected different antigens contained in the vaccines. Finally, the pre- and post-
fourth dose levels of antibodies to pertussis toxin (Ptxn), diphtheria toxin (Dtxn), and tetanus toxin (Ttxn) were compared between children with, and without, entire limb swelling to explore whether antigen–antibody interaction might explain the extensive swelling reaction.

METHODS

Subjects
The methods of these trials were published previously.3,4 Healthy 15- to 20-month-old children who had received a primary series of 1 of 13 DTaP vaccines or 1 of 2 DTwP vaccines at 2, 4, and 6 months of age in a National Institutes of Health-supported multicenter trial were invited to enroll into a fourth dose booster study in which children were given the same DTaP or DTwP as administered in the primary series. A fifth dose of the Lederle DTaP vaccine or 1 of 6 of these DTaP vaccines was administered to a subset of these children at 4 to 6 years of age. Children received a different vaccine at dose 4 or 5 if the vaccine given for the previous doses was not available. This study primarily analyzed the children who received the same vaccine for all 4 or 5 doses. The trial was conducted through the 6 National Institutes of Health supported Vaccine Evaluation Units: Baylor College of Medicine, Houston, TX; Johns Hopkins University School of Public Health, Baltimore, MD; St Louis University School of Medicine, St Louis, MO; University of Maryland School of Medicine, Baltimore, MD; University of Rochester School of Medicine, Rochester, NY; and Vanderbilt University, Nashville, TN. The study was approved by the institutional review boards of each participating center and written informed consent was obtained from a parent or guardian before enrollment.

Vaccinations
The 12 different DTaP vaccines evaluated as the toddler booster and the 6 DTaP vaccines given as the 4- to 6-year booster contained from 1 to 5 pertussis components and varying quantities of diphtheria toxoid (Dtxd), tetanus toxoid (Ttxd), and aluminum (Table 1). The 12 different DTaP vaccines evaluated as the toddler booster and the 6 DTaP vaccines given as the 4- to 6-year booster contained from 1 to 5 pertussis components and varying quantities of diphtheria toxoid (Dtxd), tetanus toxoid (Ttxd), and aluminum (Table 1). The vaccines were administered intramuscularly in a volume of .5 mL with a 1-inch needle into the anterolateral thigh in toddlers and deltoid muscle in preschool children. Oral poliovirus vaccine was the only concurrent immunization at the toddler booster; concurrent immunizations were not controlled at the fifth dose.

Reaction Assessment
Parents were given a diary card and a digital thermometer. For 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability for up to 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability 3 days after vaccination, they were asked to 1) take and record an evening temperature, 2) note the presence or absence of irritability

Serology
Antibody measurements were performed on blood samples obtained immediately before and ~1 month after the fourth dose of vaccine. For antibody to the pertussis antigens, results obtained previously1 were used in analyses. Serum diphtheria and tetanus antitoxin levels were determined at the University of Maryland in children who experienced entire thigh swelling after the fourth dose of DTaP, and in 2 randomly selected control children per case who received the same vaccine but had no thigh swelling. Neutralizing antibody to Dtxn was measured in the Vero-cell assay developed by Gupta et al10 and adapted by M. C. Anderson, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration. The assay was calibrated through use of reference antitoxin lot 451 with a unitage of 4 U/mL obtained from CBER. This antitoxin was a freeze-dried preparation of the US standard diphtheria antitoxin. Diphtheria toxin (lot 35119 from CBER) was used at a concentration of 8 Lf/mL, allowing an assay sensitivity of .01 anti-toxin U/mL. Tetanus antitoxin levels were measured by enzyme-linked immunosorbent assay by previously described methods,11 and international units were extrapolated using World Health Organization reference serum 76/589.

TABLE 1. Contents of Vaccines

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Ptxd*</th>
<th>FHA*</th>
<th>FIM*</th>
<th>PRN*</th>
<th>Aluminum</th>
<th>Dtxd†</th>
<th>Ttxn†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasteur-Mérieux (2)</td>
<td>25</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>.3</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Bioncine Slavo (3)</td>
<td>5</td>
<td>2.5</td>
<td>–</td>
<td>2.5</td>
<td>.35</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Smith-Kline Beecham Biologicals (3)†</td>
<td>25</td>
<td>25</td>
<td>–</td>
<td>8</td>
<td>.5</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Connaught Laboratories, Canada (5)</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>.3</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Swiss Serum Vaccine Institute (1)</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>.44</td>
<td>10</td>
<td>5.3</td>
</tr>
<tr>
<td>Smith-Kline Beecham Biologicals (2)</td>
<td>25</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>.5</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Ponton Products (4)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>.75</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Connaught Laboratories, Canada (4)</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>.35</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Michigan Department of Public Health (2)</td>
<td>25</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>.5</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Bioncine Slavo (1)</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>.35</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Connaught Laboratories, United States (2)†</td>
<td>23</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>.17</td>
<td>6.7</td>
<td>5</td>
</tr>
<tr>
<td>Lederle-Praxis (4)‡</td>
<td>3.5</td>
<td>35</td>
<td>0.8</td>
<td>2</td>
<td>0.23</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Lederle Whole Cell DTP</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>.1</td>
<td>12.5</td>
<td>5</td>
</tr>
</tbody>
</table>

* μg/dose. † Limit of flocculation units per dose. ‡ Licensed in the United States.
TABLE 2. Rates of Large Swelling Reactions to Booster Doses of Various DTaP Vaccines Among Children Given the Same Vaccine for All Doses

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Postdose 4</th>
<th>Postdose 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Swelling &gt;50 mm n (%)</td>
</tr>
<tr>
<td>Pasteur Mérieur (2)</td>
<td>70</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Biocine Sclavo (3)</td>
<td>71</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Smith-Kline Beecham Biologicals (3)</td>
<td>76</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>Connaught Laboratories, Canada (5)</td>
<td>75</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Swiss Serum Vaccine Institute (1)</td>
<td>81</td>
<td>6 (7.5)</td>
</tr>
<tr>
<td>Smith-Kline Beecham Biologicals (2)</td>
<td>128</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Porton Products (4)</td>
<td>73</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Connaught Laboratories, Canada (4)</td>
<td>74</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Michigan Department of Public Health (2)</td>
<td>86</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Biocine Sclavo (1)</td>
<td>64</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Connaught Laboratories, United States (2)</td>
<td>84</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Lederle-Praxis (4)</td>
<td>133</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Lederle DTP§</td>
<td>16</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

*Excludes children with entire limb swelling.

and 146 preschool children were given a mixed schedule of DTaP vaccines. Sixteen children were given a fourth dose of Lederle DTwP and 4 of these received a fifth Lederle DTwP dose. The remaining toddlers either received DTwP boosted by DTaP (n = 246) or did not participate in the booster studies (n = 991).

After the toddler booster dose, swelling of the entire thigh was reported in the comments section by parents of 20 children (2.0%) who received 4 doses of the same DTaP vaccine and 1 of the 16 children given 4 consecutive doses of DTwP (Table 2). Interestingly, entire thigh swelling was not reported in any of the 246 toddlers primed with DTwP and boosted with DTaP. None of the subjects with entire thigh swelling received their fifth dose of DTaP vaccine as part of this evaluation, because most children had already been given their preschool DTaP before this fifth dose booster study was initiated. Of the 4 children from the University of Maryland site who had entire thigh swelling after dose 4, 3 were located, however. All 3 had been given a fifth dose of a DTaP vaccine, and no severe reactions were recalled by the parents. None of the 121 children who got a fifth dose of the same vaccine were reported to have swelling of the entire deltoid, but 4 of the 146 (2.7%) children who received different DTaP vaccines throughout the series experienced such swelling. This difference is not significant (P = .13).

The number of subjects receiving consecutive doses of the same vaccines and the percentage of recipients of each vaccine with swelling >50 mm (excluding those with whole limb swelling) after doses 4 and 5 are shown in Table 2. The rates of swelling >50 mm after the fourth dose of the 12 DTaP vaccines ranged from 1.6% to 10.0%. After the fifth dose of 5 of these vaccines, the range of rates of swelling >50 mm increased to between 8.3% and 27.3%.

There were no significant differences in the rates of fever between children who did, and did not, have entire thigh swelling after dose 4 (Fig 1). More of the children with entire thigh swelling were irritable, 70% versus 37% (P = .004). Local reactions were more commonly observed in toddlers with entire thigh swelling than in those without such swelling.

Erythema was seen in 60%, versus 29% (P = .005), and local pain was judged by parents to be experienced by 60%, versus 30% of the children without entire limb swelling (P = .006). Examples of parental comments were “thigh 3 times the other one; it got so big we couldn’t believe it” and “whole leg is hard and swollen, refused to move leg; kept saying ‘sick, sick, sick.’” In fact, 4 children would not move the involved leg, and 2 were taken to their pediatrician because of the swelling and pain. Onset of swelling occurred on day 1 in 8 children, day 2 in 9 children, and day 3 in 3 children. Pain was graded to be mild in 7, moderate in 2, and severe in 3 of the 20 children with entire thigh swelling. None of the 12 children with swelling beginning on day 2 or 3 were reported to be in moderate or severe pain, whereas 5 of the 8 whose swelling began on day 1 had moderate to severe pain (P = .004). The duration of entire thigh swelling was 1 day (5 children), 2 days (3 children), 3 days (1 child), 4 days (2 children), or unknown (9 children). All reactions subsided spontaneously, completely, and without sequelae.

Entire thigh swelling was reported to have occurred after the fourth dose with 9 of the 12 DTaP vaccines, which contained from 1 to 5 pertussis components (Table 1). Relationships between the reported rates of entire thigh swelling and the quantity

http://www.pediatrics.org/cgi/content/full/105/1/e12 3 of 6
of Ptxd, Dtxd, Ttxd, and aluminum are shown in Fig 2. In separate linear regression models, rates of reported entire thigh swelling were positively associated only with Dtxd content ($P = .02$). There was a trend toward an association with Ttxd content ($P = .06$), but Ttxd content is correlated with Dtxd content in these vaccines (Pearson; $r = .6$). The amount of Dtxd contained in the vaccine remained significantly associated with swelling rates after adjustment for each other component, except for Ttxd. The comparison of the distributions of prevaccination and postvaccination antibody concentrations against Dtxn, Ttxn, and Ptxn among children with entire thigh swelling and controls showed no significant differences (data not shown). Also, the anti-Dtxn, anti-Ttxn, and anti-Ptxn antibody levels prevaccination and postvaccination were similar to the geometric mean concentration of antibody of all children given the same DTaP vaccine.

The relationship between reported rates of swelling $>50$ mm, excluding those with entire limb swelling, and the quantities of the various antigens after dose 4 and 5 were also explored by linear regression. These lesser degrees of swelling correlated not with Dtxd content but with Ptxd content after dose 4 ($P = .03$) and aluminum content after dose 5 ($P = .02$).

**DISCUSSION**

Swelling of the entire injected limb has been reported after repeated administration of a number of different vaccines, including Dtxd$^{12}$ Ttxd$^{13}$ and whole cell pertussis.$^{14}$ Acellular DTaP vaccines were developed specifically to reduce systemic and local reactions caused by DTwP vaccines. A retrospective survey of the safety of DTaP vaccine in Japan revealed swelling and erythema from the arm to the wrist in 7 (2/100 000) recipients of a third or fourth dose of DTaP.$^{15}$ Additionally, a few of the children in the early Swedish study given a third or fourth booster dose of a 2-component acellular pertussis vaccine, without Dtxd or Ttxd, also experienced swelling of the entire thigh.$^{16}$ A proposed explanation was that these acellular pertussis vaccines were given by the deep subcutaneous route, because it has been demonstrated that local reactions are both more common and more severe after subcutaneous injection of adsorbed vaccines.$^{16}$ To our knowledge, there have been only 2 previous published reports of entire thigh swelling after a fourth dose of an intramuscularly administered DTaP vaccine, and both involved vaccines from the same manufacturer.$^{8,9}$

The rates of entire limb swelling reported in this
National Institutes of Health-sponsored study probably underestimate the true incidence of such reactions. At the time that this multicenter trial of booster doses of DTaP vaccines was conducted, severe swelling had not been reported associated with DTaP injected intramuscularly. Therefore, parents were not specifically questioned about the presence of entire thigh swelling and circumstances were not measured. The rates of entire thigh swelling in this evaluation were simply those spontaneously reported by the parents to the study nurses and written in the comments section of the parent’s diary card. It has been documented that rates of spontaneously reported reactions may be ~5-fold lower than those specifically elicited by the diary card and nurses direct questioning.9 Despite this less than optimal surveillance, swelling of the entire thigh was reported to have been experienced by 2% of recipients of 4 consecutive doses of DTaP vaccines and by 1 of 16 children given DTwP vaccine. There were no reports of swelling of the entire upper arm among the 121 preschool children given a fifth consecutive dose of DTaP or DTwP vaccine injected into the deltoid. This could be because the numbers of children studied were small, as entire upper arm swelling did occur in 2.7% of children given a mixed series of DTaP vaccines. Practitioners are encouraged to report cases of severe local reactions after immunization to the Vaccine Adverse Event Reporting System (800/822-7967; www.fda.gov/cber(vaers/report.htm).

Previous reports had described the cases of entire thigh swelling as a benign reactive edema.10 In our study, 60% of children had associated erythema and 60% reported pain. Interestingly, none of the 3 children whose thigh swelling was first noted on day 2 or 3 seemed to be in moderate to severe pain, whereas 5 of the 8 with thigh swelling starting on day 1 had at least moderate pain. This suggests that there may be more than 1 pathophysiologic mechanism responsible for the swelling. Another feasible explanation is that the parents might be more likely to notice the thigh swelling if the child had significant pain, which was more likely to occur on day 1.

Entire thigh swelling occurred in children receiving a fourth dose of 9 of the 12 different DTaP vaccines evaluated. These 9 vaccines contained from 1 to 5 different pertussis components. The only vaccine components that were received by all children with severe swelling were Ptxd, Dtxd, Ttxd, and aluminum. Exploration of the relationship of rates of entire thigh swelling after dose 4 with different quantities of each component in the different vaccines revealed a significant relationship only with the quantity of Dtxd contained in the vaccine. In general, the higher the amount of Dtxd contained in the vaccine the higher the rate of entire thigh swelling. Our observation of a relationship between Dtxd content of DTaP vaccines and limb swelling is not surprising, because it has been demonstrated previously that the rate of large local reactions after DTwP vaccine were diminished but not eliminated, when the Dtxd content was reduced.17,18

Only a small percentage of children receiving any of the DTaP vaccines were spontaneously reported to have had entire limb swelling. We hypothesized that the children with entire thigh swelling might have experienced an Arthus reaction caused by high prevaccination diphtheria antitoxin levels. It was demonstrated in the 1950s that adults and adolescents with prevaccination antibodies to Dtxn experience more frequent and severe local reactions to diphtheria immunization.12,18 Subsequently, an association was found in Canadian children between large erythematous reactions and higher prevaccination neutralizing antibody to Dtxd, but no such relationship was found with severe swelling.17 The finding that both pre- and post-antibody concentrations to Dtxd, Ttxd, and Ptxd in cases and controls did not differ suggests that an Arthus reaction from preexisting high levels of serum neutralizing antibody was not an explanation for the severe swelling.

Our study showed that Dtxd content is not the explanation for lesser degrees of swelling. Swelling of >50 mm correlated not with Dtxd content but with the quantity of Ptxd given at dose 4 and with the aluminum content at dose 5. The factor(s) responsible for these smaller swelling reactions may differ from those causing entire limb swelling. Alternatively, the association of Dtxd content with entire limb swelling detected in this evaluation may not be a true biological phenomenon. The inconsistent pattern of associations of vaccine content and swelling may indicate that the associations were statistical artifact attributable to small sample size or to differential reporting of entire thigh swelling among the DTaP vaccine groups.

The pathophysiology of the range of local reactions seen after booster injections of DTaP vaccine is probably multifactorial and may be a cumulative increased response to several antigens.2 Both whole cell pertussis14,19 and Ttxd13 have been documented to cause large local reactions. Additionally, aluminum compounds, which were used as adjuvants to increase immunoglobulin G antibody responses in each of the DTaP vaccines evaluated in this study, may have a role in inducing vaccine reactions.16 Calcium phosphate adsorbed Dtxd vaccines may cause fewer adverse reactions than aluminum adsorbed vaccines.20 Additionally, serum immunoglobulin G antibodies are only 1 aspect of the immune response. Previous studies have shown an association between severe local reactions and immunoglobulin E antibody levels to the toxoid vaccines, which are enhanced by aluminum adsorption.21–23 Finally, cell-mediated immunity may play a role in sensitization of certain individuals to repeated doses of Dtxd vaccines and this was not assessed in our study.24

We believe this to be the first study to indicate a possible relationship between high Dtxd content and swelling of the entire limb after booster doses of DTaP administered intramuscularly in toddlers. Because of the lack of association of Dtxd content with lesser degrees of swelling, any extrapolations or conclusions from these data should be made with caution. However, if confirmed, the results suggest that decreasing the quantity of Dtxd in certain high diphtheria content DTaP vaccines used for booster doses might lessen the rate of entire limb swelling after
fourth or fifth doses of some DTaP vaccines. The quantity of Dtxd in vaccines used to boost immunity in adults was specifically reduced to avoid the severe local reactions experienced by individuals with pre-existing immunity, and these lowered doses of Dtxd were found adequate to elicit an anamnestic response in primed adults. The resurgence of diphtheria in Eastern Europe reminds us that it is essential that adequate immunogenicity be maintained, however. Other possible approaches to reducing local reactions include using more highly purified Dtxd or using an adjuvant that does not stimulate an immunoglobulin E antibody response. Preliminary studies of reduction of the quantities of several antigens in a combined Dtxd–Ttxd 3-component acellular pertussis vaccine suggest that this approach may successfully reduce local reactogenicity, while maintaining immunogenicity. Eventually, when new data become available on duration of protection after DTaP immunization, additional reductions in reactions may be possible through refinements in schedule.

ACKNOWLEDGMENTS

This work was supported by Contracts NO1-AI15096 (Maryland), NO1-AI05049 (Rochester), NO1-AI02645 (Vanderbilt), NO1-AI05051 (St Louis), NO1-AI72629 (Baylor), NO1-AI62515 (Hopkins) from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and by the vaccine manufacturers Chiron Vaccines, Michigan Department of Public Health, Pasteur Mérieux Connaught, SmithKline Beecham Biologicals, Speywood Pharmaceuticals (formerly Porton Products), Swiss Serum Vaccine Institute, and Wyeth-Lederle Vaccines and Pediatrics.

Dr Rennells currently is conducting vaccine trials sponsored by Wyeth Lederle Vaccines and Merck Laboratories, Inc and is a member of the Data Safety Monitoring Board for the SmithKline Beecham pediatric Lymexil trial. She has given lectures sponsored by Pasteur Mérieux Connaught, SmithKline Beecham, and Wyeth Lederle Vaccines. He is a consultant for Pasteur Mérieux Connaught and SmithKline Beecham and is receiving research funds from SmithKline Beecham. He gives lectures sponsored by Pasteur Mérieux Connaught.

Dr Losonsky is a consultant for Biocine.

Dr Englund is receiving research support from Pasteur Mérieux Connaught and is a speaker for Pasteur Mérieux Connaught and Wyeth Lederle Vaccines.

Dr Anderson has vaccine trial contracts with Pasteur Mérieux Connaught, SmithKline Beecham, and Wyeth Lederle Vaccines.

Dr D’Ennios is a consultant for SmithKline Beecham and is conducting vaccine trials for Pasteur Mérieux Connaught and Wyeth Lederle Vaccines.

Dr Edwards is a consultant for and has vaccine trial contracts with Pasteur Mérieux Connaught, SmithKline Beecham, and Wyeth Lederle Vaccines. She also gives lectures sponsored by Pasteur Mérieux Connaught and Wyeth Lederle Vaccines.

We thank the families who made this evaluation possible and the dedicated study nurses and pediatricians who cared for them.

REFERENCES


15. Isohura S. Efficacy and safety of acellular pertussis vaccine in Aichi Prefecture, Japan. Pediatr Infect Dis J. 1988;7:258–262


