Diphtheria Antitoxin Levels among Children Primed with a Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Lot with a Subpotent Diphtheria Toxoid Component

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One lot of a nationally distributed diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine was recalled in January 1999 because of a subpotent diphtheria toxoid component. To evaluate vaccine immunogenicity, children who had received the recalled lot for at least 2 of the 3 doses of their primary series were identified. Diphtheria antitoxin (DAT) levels were then prospectively assessed before and after dose 4 of (fully potent) DTaP vaccine. Of the 105 children evaluated, 84% had prevaccination DAT levels <0.10 IU/mL, which is the level generally accepted as protective. DAT levels rose a mean of 92-fold after dose 4; 100% of subjects had DAT levels ≥0.10 IU/mL, and 69% had DAT levels ≥1.0 IU/mL. These results indicate that diphtheria potency testing can identify vaccine that is less immunogenic when administered during the primary series. The booster response to dose 4, although reduced, was sufficient to confer adequate protection in the interval before receipt of the fifth dose of DTaP.

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Informed consent was obtained from the patients’ parents or guardians, and the human experimentation guidelines of the US Department of Health and Human Services were followed in the conduction of this clinical research.
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Methods
Participants were children enrolled in the Group Health Cooperative (GHC), a health maintenance organization in Washington State that has an annual birth cohort of ~3500 children. GHC has a computerized immunization tracking system in which information on vaccines administered to its members, including the type of vaccine, date of administration, manufacturer, and lot number, is recorded. Since January 1997, GHC has participated in a post-marketing surveillance assessment of Tripedia DTaP vaccine; there-
fore, this vaccine has been the DTaP vaccine routinely used at GHC. Between February 1998 and the recall in January 1999, ∼4700 doses of the recalled lot of DTaP had been administered to children at GHC.

For this study, GHC systems were used to identify children <2 years old who had been enrolled at GHC since birth, who had completed the primary DTaP series but had not yet received dose 4 of DTaP, and who had received the recalled lot for at least 2 of the 3 doses in the primary series. Blood specimens were obtained before and 1 month after the fourth dose of (fully potent) Tripedia DTaP, administered per routine practice at ∼15 months of age. Other vaccines were administered at the same visit at the discretion of the health care provider.

Serum antibody titers against diphtheria toxoid were determined by the Vero cell toxin neutralization test, a functional test that measures the ability of the test sera to protect Vero cells from a diphtheria toxoid challenge. By use of sterile 96-well microtiter plates, 2-fold dilutions of test sera, beginning with a 1:4 dilution, were challenged with diphtheria toxoid and allowed to incubate. Vero cells were added, and wells were sealed with sterile mineral oil and incubated for 6–8 days. Antibody levels then were determined by observing a color change of the pH indicator in the media that resulted from the byproducts of cell metabolism. Results are reported as international units per milliliter, after standardization with reference sera provided by the World Health Organization.

Results

We identified 320 children who met the eligibility criteria. Of those, 59 had received dose 4 of DTaP by the time they were contacted by study staff. Of the rest, consent for participation was obtained for 183 children, and, of those, pre- and postvaccination specimens were collected from 105. For these subjects, prevaccination specimens were collected between 29 March and 30 September 1999; postvaccination specimens were collected between 7 May and 3 November 1999. Of the 105 subjects, 71% percent were white, 12% Asian, and 5% black. No information on race was available for the others.

Of the 105 subjects, prevaccination DAT levels varied depending on the prevaccination DAT level. Among children with prevaccination DAT levels ≥0.01 IU/mL, the postvaccination geometric mean concentration (GMC) was 0.59 IU/mL (95% confidence interval [CI], 0.44–0.80 IU/mL); among those with prevaccination DAT levels >0.01 and ≤0.10 IU/mL, the postvaccination GMC was 1.65 IU/mL (95% CI, 1.32–2.06 IU/mL); and among those with prevaccination DAT levels >0.10 IU/mL, the postvaccination GMC was 2.89 IU/mL (95% CI, 2.11–3.96 IU/mL). All subjects with prevaccination DAT levels ≤0.01 IU/mL had a ≥32-fold increase in DAT level after vaccination, and all had postvaccination DAT levels ≥0.16 IU/mL. However, only 36% (31/87) of this group had a postvaccination DAT level ≥1.0 IU/mL, compared with 82% (61/74) of subjects with prevaccination DAT levels >0.01 IU/mL (P < .001).

There was no difference in pre- or postvaccination DAT GMC among children who had received the recalled lot for doses 1 and 2 of the primary series, compared with those who had received the recalled lot for doses 2 and 3. Pre- and postvaccination DAT GMCs also did not vary significantly by age at receipt of dose 4, interval between doses 3 and 4, or month that the subject received the first dose of the recalled lot (data not shown).

Discussion

These results support the recommendations issued in response to the recall. Among the children in our study, 84% had DAT levels <0.1 IU/mL, the level generally accepted as consistently protective [3, 4], before receipt of dose 4. Therefore, the recommendations for supplemental vaccination for children primed with ≥2 doses of the recalled lot who would be travelling to areas with high exposure to diphtheria before receipt of dose 4 were warranted.

After the booster dose of fully potent DTaP vaccine, 69% of subjects had DAT levels ≥1.0 IU/mL. DAT levels ≥1.0 IU/mL generally are accepted as indicative of more durable protection that lasts several years [3, 4]. Children with prevaccination DAT levels ≤0.01 IU/mL were less likely to achieve postvaccination DAT levels ≥1.0 IU/mL; however, all these children had postvaccination DAT levels ≥0.10 IU/mL and should be protected in the interval before dose 5. These results suggest that supplemental vaccination may not have been required for children who had received the fourth dose of DTaP, regardless of whether they had received the recalled lot during the primary series, and that they could complete the 5-dose series on the standard schedule.

We were able to conduct this assessment in response to the vaccine recall because GHC maintains an immunization da-
tabase that records information, including vaccine type and lot number, on vaccines administered to its members. This information can be used to identify potentially eligible participants for prospective assessments, such as this one, or to link with other databases that record information on clinical outcomes for retrospective epidemiologic studies. Currently, 6 managed care organizations, including GHC, collaborate with the CDC in the Vaccine Safety Datalink (VSD) project [5, 6]. The VSD project has utilized the combined database capacities of the participating organizations to conduct both prospective [7] and retrospective [8, 9] evaluations of the safety of licensed vaccines, further demonstrating the value of these managed care–based systems for population-based evaluations of the safety of vaccines in routine use.

One limitation of our study is that we did not evaluate the DAT response to dose 4 among a comparable group of children who had received fully potent Tripedia vaccine for all doses of the primary series. However, comparison with the results of previous assessments of the vaccine suggests that our DAT levels before and after dose 4 were lower than would be expected for children primed with fully potent vaccine. In one study of 88 children who had received dose 4 of Tripedia vaccine after having been primed with the same vaccine, mean pre- and postvaccination DAT levels were 1.2 and 6.8 IU/mL (95% CIs not provided) [10]. In a more recent assessment of the immunogenicity of dose 4 of DTaP, pre- and postvaccination DAT GMCs for 10 subjects who had received Tripedia for all 4 doses were 2.5 IU/mL (95% CI, 1.1–5.6 IU/mL) and 5.1 IU/mL (95% CI, 3.0–8.5 IU/mL) [11]. In an assessment of 160 children who had received a whole-cell diphtheria and tetanus toxoids and pertussis vaccine for the primary series and Tripedia for dose 4 at age 18 months, pre- and postvaccination DAT GMCs for dose 4 were 0.32 IU/mL and 14.72 IU/mL, respectively [12]. Our mean pre- and postimmunization DAT levels of 0.027 and 1.34 IU/mL suggest that receipt of the recalled lot for 2 doses of the primary series was associated with a substantially diminished DAT response to the primary series and with a reduced response to dose 4. This indicates a concordance between the results of the potency testing and the immunogenicity of the diphtheria toxoid component of the recalled lot of vaccine.

Other limitations of our study include that we assessed only the response to a booster dose of Tripedia. Thus, we cannot generalize these findings to children primed with the recalled lot who then received another DTaP vaccine for the booster dose. In addition, the kinetics of the decline in diphtheria potency of the recalled lot are not known; therefore, it is possible that response to the diphtheria toxoid component of the vaccine may have varied depending on when the vaccine was administered. Since most of the doses (77%) of the recalled lot administered to children in our study were given over a fairly short interval (from May through August 1998), our ability to assess variation in immunogenicity by date of administration was limited.

In summary, the results of this assessment indicate that diphtheria potency testing can identify vaccine that is less immunogenic when administered during the primary series. If such a vaccine has been distributed, measures to ensure that recipients are not at increased risk of disease are warranted. Children who have received vaccine during the primary series that is subpotent but that has some potency remaining can have an acceptable DAT response to dose 4.

References