

# Absence of an Increase in Cardiorespiratory Events After Diphtheria-Tetanus-Acellular Pertussis Immunization in Preterm Infants: A Randomized, Multicenter Study

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## What's Known on this Subject

Several studies, using historical controls and subjective observations, have reported an increased incidence of prolonged apnea and bradycardia after DT-P vaccine in preterm infants. This has resulted in delays in vaccine administration to this vulnerable group of infants.

## What This Study Adds

This randomized, controlled clinical trial, using physiologic recordings of cardiorespiratory events in preterm infants after DT-P vaccine found no increase in prolonged apnea and bradycardia after immunization.

## ABSTRACT

**OBJECTIVE.** The American Academy of Pediatrics recommends immunization of preterm infants at 2 months' chronological age with diphtheria-tetanus-acellular pertussis vaccine, regardless of birth weight and gestational age. Several investigators have reported an increased incidence of cardiorespiratory events in preterm infants after immunization. Consequently, many primary care providers do not adhere to American Academy of Pediatrics guidelines. The purpose of this study was to reexamine the relationship between diphtheria-tetanus-acellular pertussis and cardiorespiratory events in preterm infants by using a random control study design and an objective assessment of cardiorespiratory events.

**METHODS.** Ten hospitals enrolled 191 infants who were born at <37 weeks' gestational age at 56 to 60 days' chronological age. Infants were randomly assigned to a group that received diphtheria-tetanus-acellular pertussis immunization ( $n = 93$ ) or a control group that did not ( $n = 98$ ). Recording monitors were used continuously during the next 48 hours to document prolonged apnea and prolonged bradycardia. The presence and number of episodes during the 48-hour period were compared between groups by using  $\chi^2$  and  $t$  tests.

**RESULTS.** In the diphtheria-tetanus-acellular pertussis group, 16.1% experienced at least 1 episode of prolonged apnea compared with 20.4% of control infants. One or more prolonged bradycardia events occurred in 58.1% of immunized infants and 56.1% of the control infants. The frequency of episodes was not significantly different between groups. The immunization group and the control group each had an average of 0.5 episodes of prolonged apnea. The mean number of prolonged bradycardia episodes was 2.6 in the immunization group and 2.7 in the control group.

**CONCLUSIONS.** Preterm infants who received diphtheria-tetanus-acellular pertussis at 2 months after birth were no more likely to experience prolonged apnea and bradycardia than were control infants. This study supports the American Academy of Pediatrics recommendation regarding diphtheria-tetanus-acellular pertussis immunization at 2 months of age for preterm infants.

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This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT00482781).

### Key Words

apnea, bradycardia, immunization, DTaP, preterm infant

### Abbreviations

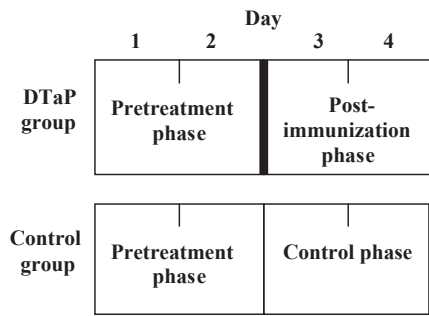
AAP—American Academy of Pediatrics  
DTaP—diphtheria-tetanus-acellular pertussis  
bpm—beats per minute

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**T**HE AMERICAN ACADEMY of Pediatrics (AAP) recommends that preterm infants begin routine diphtheria-tetanus-acellular pertussis (DTaP) immunization with full doses at 2 months of chronologic age, regardless of gestational age or birth weight.<sup>1</sup> Practice differences among primary care providers persist regarding adherence to these recommendations,<sup>2-4</sup> and preterm infants, although at increased risk for vaccine-preventable diseases, often receive immunizations in reduced dosages or on a delayed schedule.<sup>2</sup>



**FIGURE 1**  
Study design. During the 4 days of the study, infants in each group had recordings made to document apnea and bradycardia. At the end of day 2, after the 48-hour pretreatment phase, infants in the DTaP group received their immunizations. Infants in the control group were immunized at the end of the second 48-hour study period. Heavy vertical lines show time of immunization.

Case reports of severe apnea requiring resuscitation after immunization initiated concerns regarding possible deleterious effects among preterm infants.<sup>5</sup> Numerous studies subsequently reported an increased incidence in apnea and bradycardia after the DTP immunization of these infants.<sup>6–13</sup> Whereas early reports pertained to the whole-cell pertussis component,<sup>6–9</sup> more recent studies reported increased apnea and bradycardia with acellular pertussis as well.<sup>10–13</sup> Only 1 study to date has not reported an increase in apnea and bradycardia in preterm infants after immunization.<sup>14</sup> Unfortunately, previous studies used clinical observations, possibly subject to observer bias, and historical controls. The objective of our study was to examine the relationship between DTaP immunizations and cardiorespiratory episodes while using a randomized, controlled study design and an objective measurement with verification of the frequency and severity of cardiorespiratory events.

## METHODS

This randomized, blinded, controlled clinical trial was conducted in 10 NICUs within the United States between September 1, 2000, and September 30, 2004. Institutional review board approval was obtained for each participating center. The study population consisted of preterm infants, born at a gestational age <37 weeks, who were 2 months' chronologic age ( $\geq 56$  days and  $\leq 60$  days) at time of study entry. All infants remained in the NICU for at least 6 days after enrollment. Infants were considered ineligible for participation, in either study group, when they had active infections, were critically ill, or had unstable vital signs. The decision to initiate vaccination, based on clinical stability, was made by the attending neonatologist. Infants who required assisted ventilation or tracheostomy during the study were excluded from participation. Parental/caregiver consent for enrollment was obtained in writing for all infants.

The basic study design is shown in Fig 1. On enrollment into the study, patients were assigned randomly (by random number assignment) into either the DTaP group or the control group. During the initial 2-day period of the study and subsequent to group assignment,

both groups were treated similarly (pretreatment phase). On day 3, after completion of the pretreatment phase, the DTaP group was immunized with either Infanrix or Pediarix (SmithKline Beecham Biologicals, Pittsburgh, PA). The control group was not immunized until the end of day 4 of the study. The heavy vertical lines represent the timing of immunization. The NICU nurse caring for the infant administered a 0.5-mL dose of the vaccine intramuscularly in the anterolateral thigh.

Throughout the 4-day study, apnea and bradycardia were recorded using bedside event-recording capable monitors (Healthdyne Smart Monitor [Respironics, Murrysville, PA]). These detect central apnea using thoracic impedance and bradycardia using both electrocardiography and beat-to-beat heart rate recording. The monitors were set to alarm and record all respiratory pauses of  $\geq 15$  seconds and 10-second averaged heart rate declines to  $\leq 80$  beats per minute (bpm). The information stored within the monitor was downloaded at the end of the pretreatment phase (end of day 2) and again at the end of the immunization/control phase (end of day 4). Each of the monitor downloads was assigned a nonsequential code number. Downloads were forwarded, in bulk, to 2 analysts (Drs Kelly and Steinschneider) for independent interpretation. In this manner, the analysts were blinded to the download group and phase status.

Standard definitions were applied by using the *Monitor Alarm/Event Recordings (Respiration and ECG): Descriptive Terminology* manual.<sup>15</sup> Prolonged apnea was defined as a respiratory pause of  $\geq 20$  seconds in duration or  $\geq 15$  seconds in duration when associated with bradycardia ( $\leq 80$  bpm) for at least 5 seconds. Prolonged bradycardia was defined as a heart rate of  $< 80$  bpm that lasted  $\geq 10$  seconds. Severe events were defined as a respiratory pause for  $\geq 30$  seconds in duration or a bradycardia of  $\leq 60$  bpm for at least 10 seconds. Interscorer reliability was determined by calculating the percentage of alarm events agreed on by the 2 analysts. Any discrepancies in event scoring were resolved after discussion by the analysts, and a single event score was agreed on.

A sample size of 100 infants was required in each of the 2 groups to achieve 80% power in detecting significant differences in the occurrence of prolonged apnea and prolonged bradycardia episodes between the DTaP and control groups. A data form was completed for each infant, consisting of biographical data, maternal data, infant medical data, and immunization information. Statistical analyses were performed by using SAS (SAS Institute Inc, Cary, NC) and StatPac (StatPac, Inc, Bloomington, MS). Differences in patient and treatment characteristics between the experimental (DTaP immunization) and control groups were evaluated by using  $\chi^2$  and *t* tests of significance. Differences in the outcome data were assessed in 2 ways. The occurrence of prolonged events (apnea, bradycardia, or either event) was calculated as the percentage of infants with  $\geq 1$  event, and  $\chi^2$  testing compared the experimental and control groups. The average number of prolonged apnea, prolonged bradycardia, or either event was compared by using *t* tests. In addition, the percentage of infants with

**TABLE 1 Infant Characteristics**

Characteristic	DTaP Group (n = 93)	Control Group (n = 98)	P <sup>a</sup>
Gestational age at birth, wk	26.9 (26.5–27.2)	27.0 (26.5–27.5)	.57
Birth weight, g	895.7 (851.1–940.2)	935.9 (855.9–1015.8)	.38
Birth length, cm	34.1 (33.6–34.7)	34.2 (33.4–35.0)	.96
Birth head circumference, cm	24.1 (23.7–24.5)	24.4 (23.8–25.1)	.42
Male, %	53.8 (43.1–64.2)	43.9 (33.9–54.3)	.17
Multiple birth, %	23.7 (15.5–33.6)	20.4 (12.9–29.7)	.59
Respiratory distress syndrome, %	97.8 (92.4–99.7)	95.9 (89.8–98.9)	.44
Chronic lung disease, %	80.4 (70.9–88.0)	73.7 (63.7–82.2)	.27
Intraventricular hemorrhage, %	30.4 (21.3–40.9)	29.9 (21.0–40.0)	.94
Treated for apnea of prematurity, %	37.6 (27.8–48.3)	46.9 (36.8–57.3)	.19
Provided HiB immunization, %	2.2 (0.8–5.1)	4.1 (0.1–8.0)	.45

Data are means (95% confidence intervals [CIs]). HiB indicates *Haemophilus influenzae* type B.

<sup>a</sup> The *t* test was used to compare mean value of characteristic in the DTaP group with that in the control group;  $\chi^2$  test was used to compare proportion of infants with characteristic in the DTaP group with that in the control group.

$\geq 1$  severe event was compared between the 2 groups by using  $\chi^2$ . Data are presented as mean and 95% confidence interval or as a proportion and 95% confidence interval. Statistical significance is defined as  $P \leq .05$ .

## RESULTS

A total of 240 preterm infants were enrolled, and 197 infants completed the study. A total of 43 patients dropped out of the study. Six were discharged from the NICU before the study was completed, 9 were taken out of the study by their parents, 7 became medically unstable, and 21 did not complete the study because of equipment problems. The reasons for dropping out were similar for the DTaP and control groups. Six infants were not included in the analysis because of incomplete recordings, resulting in 191 infants with complete data.

Infant characteristics are shown in Table 1. The mean gestational age at birth of infants in the DTaP group was 26.9 weeks (range: 23–33 weeks) and in the control group was 27.0 weeks (range: 24–36 weeks). The mean birth weight of infants in the DTaP group was 896 g (range: 463–1788 g) and in the control group was 936 g (range: 502–2928 g). No significant differences were seen between the 2 groups with regard to gestational age at birth, birth weight, length, head circumference, gender, and the incidence of multiple gestations.

The medical characteristics of the infants with regard to the incidence of disease states were also similar (Table 1). Respiratory distress syndrome, chronic lung disease,

sepsis, and intraventricular hemorrhage, frequently associated with extreme prematurity, did not differ between the DTaP and control groups. The number of infants being treated for apnea of prematurity also was not significantly different between the 2 groups.

Table 2 summarizes the maternal characteristics of the 2 groups. No significant differences between the groups were seen regarding maternal age at delivery; smoking and drug use during pregnancy; and the presence of maternal preeclampsia, eclampsia, and gestational diabetes.

The infant characteristics at the start of event recordings are shown in Table 3. The mean postconceptional age for the DTaP group was 34.9 weeks and for control subjects was 35.1 weeks. The mean weight at initiation of event recordings for the experimental group was 1775 g and for the control group was 1766 g. The 2 groups were not statistically different at the initiation of the recordings. Table 3 also shows the percentage of infants who had prolonged apnea or prolonged bradycardia in the pretreatment phase. Again, the 2 groups were not significantly different.

Both groups of infants spent a mean of 46.9 hours on the event-recording monitors during the treatment phase of the study. Interobserver reliability in the interpretation of the event recordings was high and not significantly different between the groups (96.5% for the DTaP group and 98.2% for the control group).

**TABLE 2 Maternal Characteristics**

Characteristic	DTaP Group (n = 93)	Control Group (n = 98)	P <sup>a</sup>
Age at delivery, y	27.6 (26.2–28.9)	28.2 (26.9–29.5)	.51
Smoked during pregnancy, %	16.7 (9.6–26.0)	16.5 (9.7–25.4)	.97
Drug use during pregnancy, %	6.6 (2.5–13.8)	9.2 (4.3–16.7)	.51
Preeclampsia, %	17.4 (10.3–26.7)	10.2 (5.0–18.0)	.15
Eclampsia, %	2.2 (0.3–7.7)	4.4 (1.2–10.9)	.41
Gestational diabetes, %	6.5 (2.4–13.5)	7.3 (3.0–14.5)	.82

Data are means (95% CIs).

<sup>a</sup> The *t* test was used to compare mean age at delivery in the DTaP group with that in the control group;  $\chi^2$  test was used to compare proportion of women with characteristic in the DTaP group with that in the control group.

**TABLE 3 Characteristics at Start of Recording**

Characteristic	DTaP Group (n = 93)	Control Group (n = 98)
Chronological age, d <sup>a</sup>	57.5 (57.2–57.8)	57.9 (57.6–58.2)
Postconceptional age, wk <sup>a</sup>	34.9 (34.5–35.3)	35.1 (34.6–35.6)
Weight at start of recording, g <sup>a</sup>	1774.6 (1684.0–1865.1)	1765.7 (1643.0–1888.4)
Had prolonged apnea and/or prolonged bradycardia during pretreatment phase, % <sup>b</sup>	53.4 (42.5–64.1)	62.5 (52.0–72.2)

Data are means (95% CIs).

<sup>a</sup> The *t* test comparing mean value of characteristic in the DTaP group with that in the control group,  $P > .05$ .

<sup>b</sup>  $\chi^2$  test comparing proportion of infants who had apnea and/or bradycardia in the DTaP group with that in the control group,  $P > .05$ .

Table 4 summarizes the percentage of infants who had  $\geq 1$  event of prolonged apnea, prolonged bradycardia, or either prolonged apnea or prolonged bradycardia. Prolonged apnea was seen in 16.1% of infants who received DTaP and 20.4% of control subjects ( $P > .05$ ). Among infants in the DTaP group, 58.1% had prolonged bradycardia, whereas 56.1% of control subjects had prolonged bradycardia ( $P > .05$ ). Prolonged bradycardia was a much more frequent event than prolonged apnea in our population, with no significant difference in occurrence between the DTaP and control groups. There was also no significant difference in the percentage of infants who had either prolonged apnea or prolonged bradycardia. In the DTaP group, 59.1% had either event, compared with 58.2% in the control group.

Severe events are also summarized in Table 4. Whereas severe apnea occurred infrequently (3%), severe bradycardia was found in  $\sim 50\%$  of study infants. Again, there was no difference in the DTaP group versus the control group in either severe apnea (2.2% and 5.1%, respectively) or severe bradycardia (54.8% and 50.0%, respectively).

The study design permitted using the intervention group as its own control. We found no differences when we compared the outcomes in the intervention group for the 48 hours before vaccine administration with the 48 hours after vaccination. The percentage of infants who had prolonged apnea before immunization was 20.4% versus 19.1% after immunization ( $P > .05$ ), whereas the percentage was 53.2% before immunization versus 55.9% after immunization for prolonged bradycardia ( $P > .05$ ).

## DISCUSSION

This prospective, randomized, multicenter study found that extremely preterm infants who received DTaP at 2

months of chronological age were no more likely to experience prolonged episodes of apnea and bradycardia than were randomly assigned control subjects who were not immunized during the study period. This study, conducted in 10 NICUs in the United States during a 4-year period, involved a group of infants who were at increased risk for significant cardiorespiratory events. The study population clearly represented an extremely vulnerable group of infants, as indicated by their gestational age, birth weight, and the high incidence of the common complications of marked prematurity (respiratory distress syndrome, chronic lung disease, sepsis, and intraventricular hemorrhage). The vulnerability of the study population is also demonstrated by the high incidence of both prolonged apnea and prolonged bradycardia, as well as the high incidence of severe cardiorespiratory events: more than half of all infants experienced heart declines to  $< 60$  bpm for at least 10 seconds. Nonetheless, after blinded analysis of more than 3200 hours of event recordings by 2 reviewers with a high degree of interobserver reliability, no differences in cardiorespiratory events were found between these medically fragile infants who received DTaP and those who did not.

The AAP recommends the immunization of preterm infants with the DTaP vaccine at 2 months of chronological age, regardless of birth weight and gestational age.<sup>1</sup> This recommendation has remained consistent since 1982; however, several investigators have reported that primary care providers often do not adhere to the AAP guidelines. Magoon et al<sup>2</sup> reported immunization delays in 30% to 77% of infants, with the timing of delays ranging from 6 to 40 weeks. They found that the less the birth weight and gestational age, the greater the probability of delay. Langkamp et al<sup>3</sup> reported that very low birth weight infants ( $< 1500$  g) were less likely to be up-to-date for all immunizations at ages 12, 24, and 36 months compared with infants with higher birth weights. DTaP immunizations have also been administered to preterm infants in reduced dosages that are ineffective.<sup>2,4</sup>

Slack and Shapira<sup>5</sup> published case reports of 4 preterm infants who developed severe apneas that required resuscitation after immunizations. Many studies using historical controls subsequently supported an association between DTP immunization in preterm infants and prolonged apnea and bradycardia.<sup>6-12</sup> Although earlier studies<sup>6-9</sup> used the whole-cell component of the pertussis vaccine, more recent studies reported increased apnea and bradycardia with acellular pertussis as well.<sup>10-13</sup> Sanchez et al<sup>8</sup> published the first prospective study of the incidence of apnea and bradycardia after DTP immunization in 1997. No control group was used. They found that 30% of the infants had significant post-DTP events. They advocated the need to monitor closely very preterm infants after DTP immunization, a recommendation echoed by other groups of investigators who reported significant apnea and bradycardia.<sup>8,9</sup> Pfister et al<sup>10</sup> were the first to report mostly benign, although frequent, cardiorespiratory events after DTaP; however, they relied on historical controls and clinical observa-

**TABLE 4 Apnea and Bradycardia in DTaP and Control Groups**

Characteristic	DTaP Group (n = 93)	Control Group (n = 98)
% of infants with $\geq 1$ event		
Prolonged apnea, % <sup>a</sup>	16.1 (9.3–25.2)	20.4 (12.9–29.7)
Prolonged bradycardia, % <sup>b,c</sup>	58.1 (47.4–68.2)	56.1 (45.7–66.1)
Either event, % <sup>b</sup>	59.1 (48.5–69.2)	58.2 (47.8–68.1)
No. of events		
Prolonged apnea <sup>a,d</sup>	0.5 (0.2–0.9)	0.5 (0.2–0.7)
Prolonged bradycardia <sup>c,d</sup>	2.6 (1.7–3.5)	2.7 (1.8–3.5)
Either event <sup>d</sup>	2.9 (1.9–3.9)	2.9 (2.0–3.8)
% of infants who had $\geq 1$ severe event		
Infants who had $\geq 30$ s of apnea <sup>b</sup>	2.2 (0.3–7.6)	5.1 (1.7–11.5)
Infants who had bradycardia of $\leq 60$ bpm <sup>b</sup>	54.8 (44.2–65.2)	50.0 (39.7–60.3)

Data are means (95% CIs).

<sup>a</sup> Prolonged apnea defined as a respiratory pause  $\geq 20$  seconds in duration or  $\geq 15$  seconds in duration when associated with bradycardia ( $\leq 80$  bpm) for at least 5 seconds.

<sup>b</sup>  $\chi^2$  test comparing proportion of infants with characteristic in the DTaP group with that in the control group,  $P > .05$ .

<sup>c</sup> Prolonged bradycardia defined as a heart rate of  $< 80$  bpm that lasted  $\geq 10$  seconds. Severe events were defined as a respiratory pause of  $\geq 30$  seconds in duration or a bradycardia of  $\leq 60$  bpm for at least 10 seconds.

<sup>d</sup> T test comparing mean value of characteristic in the DTaP group with that in the control group,  $P > .05$ .



tions. Like many of the published reports regarding immunizations in preterm infants, *Haemophilus influenzae* type B vaccine was administered simultaneously, providing a possible confounding variable.<sup>7-9,11-14</sup> As recently as 2005, investigators continued to advocate close monitoring of all very preterm infants after immunization, suggesting potential adverse effects. The first study to report no substantial change in the incidence of apnea after immunizations in very preterm infants was Ellison et al.<sup>14</sup> This study consisted of a retrospective chart review, and no control group was present. Lee et al.<sup>13</sup> published a study on the frequency of cardiorespiratory events after immunizations in hospitalized preterm infants using a control group. They reported an increased incidence in adverse events, based on subjective clinical assessments by nurses and the nonsystematic routine use of standard NICU monitors, without any recording of events.

The major strengths of the current study are (1) the use of a randomized simultaneous control study design, which allowed for the control of known and unknown confounders; (2) the use of bedside event-recording monitors to assess objectively the frequency, duration, and severity of cardiorespiratory events; and (3) scoring of each monitor event recording by 2 independent analysts who interpreted the recordings blinded to the group or study phase status of the patients.

Our study is the first randomized, blinded, controlled clinical trial to use physiologic recordings of events to compare the incidence of prolonged apnea and prolonged bradycardia in preterm infants who had DTaP immunization versus those who did not. This represents a major advantage over all previous studies in permitting objective assessments of the frequency, duration, and severity of these events after DTaP vaccination, compared with a prospectively randomized control group.

Our study was powered to detect significant differences in the occurrence of either prolonged apnea or prolonged bradycardia between the DTaP and control groups. The available sample size permitted the detection of at least an 89% increase in the proportion of infants with prolonged apnea and at least a 35% increase in the proportion of infants with prolonged bradycardia.

The study design required the continuous use of event recording equipment on preterm infants in NICUs for an extended period of time. Unfortunately, this resulted in a high dropout rate (18%), mostly as a result of technical difficulties involving the equipment. All infants were similar in gestational age and chronologic age. Both the number of dropouts and the reason for dropping out were similar for the DTaP and control groups, so we do not suspect that the results were subject to bias. Nonetheless, we acknowledge the high dropout rate as a limitation of our study.

Because this clinical trial was conducted with preterm infants who remained hospitalized at 2 months of age, these results cannot be generalized to preterm infants in general. Another limitation is that there was no follow-up after NICU discharge and no long-term observation of an untreated control group. It is therefore unclear

to what extent these event recordings correlate with risk for later clinically significant events.

## CONCLUSIONS

Our results support and validate the long-standing AAP recommendations for immunization of preterm infants at 2 months of chronological age. On the basis of these cardiorespiratory event recordings, clinicians should be reassured that there is no apparent rationale for unnecessary delays in the administration of DTaP immunizations even to very preterm infants.

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