Primary Immunization of Premature Infants with Gestational Age <35 Weeks: Cardiorespiratory Complications and C-Reactive Protein Responses Associated with Administration of Single and Multiple Separate Vaccines Simultaneously

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Objective To determine the incidence of cardiorespiratory events and abnormal C-reactive protein (CRP) level associated with administration of a single vaccine or multiple separate vaccines simultaneously.

Study design Prospective observational study on 239 preterm infants at ≥2 months of age in the neonatal intensive care unit (NICU). Each infant received either a single vaccine or multiple vaccines on one day. CRP levels and cardiorespiratory manifestations were monitored for 3 days following immunization.

Results Abnormal elevation of CRP level occurred in 85% of infants administered multiple vaccines and up to 70% of those given a single vaccine. Overall, 16% of infants had vaccine-associated cardiorespiratory events within 48 hours postimmunization. In logistic regression analysis, abnormal CRP values were associated with multiple vaccines (OR, 15.77; 95% CI 5.10-48.77) and severe intraventricular hemorrhage (IVH) (OR, 2.28; 95% CI 1.02-5.13). Cardiorespiratory events were associated marginally with receipt of multiple injections (OR, 3.62; 95% CI 0.99-13.25) and significantly with gastroesophageal reflux (GER) (OR, 4.76; 95% CI 1.22-18.52).

Conclusion CRP level is expected to be elevated in the 48 hours following immunization. In a minority of infants immunized, cardiorespiratory events were associated with presumed need for intervention. Underlying medical conditions and possibly multiple injections are associated with cardiorespiratory events. Precautionary monitoring following immunizations is warranted. *(J Pediatr 2007;151:167-72)*

Based on recommendation by the American Academy of Pediatrics (AAP),[1] all premature or low birth weight (BW) infants should be immunized at approximately 2 months postnatal age regardless of gestational age (GA) and BW. Because of increased reactogenicity and several reports of cardiorespiratory events such as apnea, bradycardia, or decreased in oxygen saturation in preterm infants following primary immunization with whole-cell pertussis-based vaccines,[2-8] in January 1996, the AAP[9] recommended the use of acellular pertussis vaccine as the preferred vaccine for all infants beginning at 2 months of age. The diphtheria-tetanus-acellular pertussis (DTaP)-based combination vaccines also have become available for the purpose of reducing the amount of adjuvant and the number of intramuscular injections in infants.[10-13] Schloesser et al[14] reported no incidence of apnea after simultaneous separate immunization with DTaP and *Haemophilus influenzae* type b conjugate (Hib) in premature infants who received their vaccines in the clinics. On the other hand, Schulzke et al[12] reported a 13% incidence of cardiorespiratory events following immunization with DTaP-based combination vaccines in premature infants in the neonatal intensive care unit (NICU). Cardiorespiratory events have been reported more frequently (23% to 47%) in smaller and/or less clinically stable premature infants following primary immunization with DTaP-based vaccines.[10-13,15,16]

AAP	American Academy of Pediatrics	GER	Gastroesophageal reflux
AOP	Apnea of prematurity	HBV	Hepatitis B vaccine
BPD	Bronchopulmonary dysplasia	Hib	*Haemophilus influenzae* type b conjugate
BW	Birth weight	IPPV	Intermittent positive pressure ventilation
CPAP	Continuous positive airway pressure	IPV	Inactivated poliovirus vaccine
CRP	C-reactive protein	IVH	Intraventricular hemorrhage
DTaP	Diphtheria-tetanus-acellular pertussis	NICU	Neonatal intensive care unit
DTwP	Diphtheria-tetanus-whole cell pertussis	PCV7	Pneumococcal 7-valent conjugated vaccine
GA	Gestational age		

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Vaccination-associated adverse reactions are not uncommon and may resemble serious infection in infants. C-reative protein (CRP) is a marker of inflammation or infection in neonates.[17] A consistent increase in CRP has been reported after immunization of preterm infants with vaccines containing diphtheria-tetanus-whole cell pertussis (DTwP)[8]; however, CRP responses to DTaP and other vaccines have not been studied.

We hypothesized that in premature infants, primary immunization with DTaP will not be associated with cardiorespiratory events or with abnormal CRP. Furthermore, we also hypothesized that cardiorespiratory events and abnormal CRP values would be more likely to occur with multiple vaccines given simultaneously than with administration of any single vaccine.

METHODS

The study was approved by the Institutional Review Board of The University of Tennessee Health Science Center, and it was carried out at Rout Center for Women and Newborns from July 2001 to July 2004. Written parental consent was obtained. Subjects for the study were premature infants ≥2 months' postnatal age, who were still in the NICU and were scheduled to receive immunization. Immunization was postponed in infants who were acutely ill, had bacterial infection, or for other reasons as judged by the attending physician. The study was prospective observational and quasi-experimental, and it used a convenience sample. A group of 15 consecutive infants received a randomly chosen single vaccine from five vaccines (DTaP, Hib, inactivated poliovirus vaccine [IPV], hepatitis B vaccine [HBV], or pneumococcal 7-valent conjugate vaccine [PCV7]) or multiple separate vaccines simultaneously. For the single vaccine group, the randomization scheme used multiple blocks of random sequences of five vaccines. To have an adequate number of infants assigned to each single vaccine, every third group of 15 infants was assigned to receive multiple vaccines. In the single vaccine group, infants were given the assigned single vaccine, were monitored for cardiorespiratory events, and were given the remaining vaccines in the primary immunization 3 days later after the end of the monitoring period. Only the administration of the first vaccine in the single vaccine group was considered as part of the study. When assigned to receive multiple vaccines, infants were given two or more vaccines simultaneously in a single day. Thus, an infant was a subject in either the multiple or the single vaccine group.

Vaccines in primary immunization included: DTaP (Infanrix, SK Beecham, Philadelphia, Pa), Hib (ActHIB, Aventis, Swiftwater, Pa), HBV (Engerix-B, SK Beecham, Philadelphia, Pa), IPV (Inactivated-IPOL™, Aventis, Swiftwater, Pa), and PCV7 (Prevnar, Lederle, Pearl River, NY). Vaccines were given intramuscularly with separate syringes on the anterolateral aspect of the left or right thigh using a 5/8-inch long 25-gauge needle. The nurses administering the vaccines were not masked to the type or the number of vaccines given. All infants received acetaminophen 10 mg/kg by mouth before immunization and then every 6 hours within the first 48 hours of immunization. Outcomes examined in this study were cardiorespiratory events and abnormal CRP values observed within 3 days following immunization.

All infants were maintained on cardiorespiratory and pulse oximetry monitoring. As part of the NICU immunization protocol, infants were clinically assessed and cardiorespiratory events (apnea, bradycardia, or O_2 desaturation episodes) were documented. Apnea was defined as respiratory pauses >20 seconds; bradycardia referred to decreases in heart rate <85 beats per minute; and desaturation episodes referred to decreases in O_2 saturation to <85% with associated cyanosis. The interventions such as tactile-stimulation, initiation of O_2 supplementation, bag-mask ventilation, continuous positive airway pressure (CPAP), or intermittent positive pressure ventilation (IPPV), and also, increase in supplemental oxygen, CPAP, or ventilator settings, that the infant received because of cardiorespiratory events were documented in the infant's electronic medical record.

Those who developed cardiorespiratory events were evaluated for septicemia and given antibiotic therapy at the discretion of the attending physician. As per our NICU policy, based on our published experience,[8] if the CRP value before immunization was normal, immunization was given and CRP testing was repeated every 12 hours × 3. If the CRP became abnormal after the immunization, CRP testing was repeated daily until values became normal. Serum CRP was measured by Vitros CRP Slides methodology (Vitros 250 Chemistry System, Ortho-Clinical Diagnostics, Inc., Johnson & Johnson Co. Raritan, NJ). The level of detection was ≥0.7 mg/dL. A CRP level >1.6 mg/dL was considered abnormal.[18]

Statistical Methods

We expressed descriptive data as median, mean, and standard deviation or as frequency and percent. The t test, analysis of variance, and χ^2 test were used to compare the different vaccines and to compare the infants who received a single vaccine with those who received multiple vaccines. A multivariable logistic regression was used to determine the significance of the relationship between vaccines (single or multiple) and the outcome variables, cardiorespiratory events, and abnormal CRP values, adjusted for factors, namely: GA, sex, race/ethnicity, age at immunization, cardiorespiratory condition at immunization, diuretics, need for supplemental oxygen, and diagnosis of bronchopulmonary dysplasia (BPD), symptomatic gastroesophageal reflux (GER), intraventricular hemorrhage (IVH; grade 3 or 4), and apnea of prematurity (AOP). BPD was defined as persistent requirement for oxygen beyond 36 weeks of postmenstrual age.[19] AOP was defined as a respiratory pause of ≥20 seconds, usually associated with heart rate ≤80 beats/minute, for which no other cause could be identified.[20] Symptomatic GER was defined as

Table I. Characteristics of immunized premature infants (n = 239)

	Single vaccine n = 168 (70%)	Multiple vaccines n = 71 (30%)	P value
Sex (Male)	101 (60%)	39 (55%)	.46
Race (white)	45 (27%)	14 (20%)	.20
GA (wk, mean ± SD/median)	28.3 ± 2.8/28.0	28.4 ± 2.6/28.0	.75
BW (g, mean ± SD/median)	866 ± 292/807	864 ± 247/853	.96
Age at immunization (d, mean ± SD/median)	71 ± 20/64	71 ± 23/65	.99
Bronchopulmonary dysplasia (BPD)	143 (85%)	65 (92%)	.18
Apnea of prematurity (AOP)	65 (39%)	41 (58%)	.007
Gastroesophageal reflux (GER)	11 (7%)	12 (17%)	.01
Intraventricular hemorrhage (grade 3 & 4)	29 (17%)	17 (24%)	.23
BPD/AOP/GER/IVH*	153 (91%)	68 (96%)	.21
Oxygen at immunization	79 (47%)	26 (37%)	.14
Positive pressure ventilation at immunization	10 (6%)	1 (1%)	.18
Diuretics at immunization	67 (40%)	36 (51%)	.12
Coritcosteroid use at immunization	5 (3%)	4 (6%)	.46

*Any one or more of those diagnoses.

"spitting" or emesis associated with apnea and bradycardia that presented within an hour of feeding that was confirmed radiologically and treated pharmacologically. We chose not to adjust for both GA and BW because of problems with colinearity; we ran separate models using each and found similar results.

RESULTS

Two hundred fifty-five premature infants received immunization during the study period. Data were obtained and analyzed in 239 infants. Sixteen infants were excluded from analysis because of GA >35 weeks, or they received the 4-month or second series of immunization. Table I compares the characteristics of infants who received single versus multiple vaccine. One hundred sixty-eight infants (70%) were in a single vaccine group (DTaP n = 41; Hib n = 27; PCV7 n = 26; IPV n = 30; HBV n = 44), and 71 infants (30%) were in multiple vaccines group. BW was <1000 g in 76% of study infants. Fifty-three infants (22%) were 70 to 99 days of age, and 26 infants (11%) were 100 days of age or older at the time of first immunization. More infants with diagnosis of AOP (P = .007) and GER (P = .013) received multiple vaccines compared with single vaccines. In the group administered multiple vaccines simultaneously, 82% (58/71) of infants received all five vaccines, 10% (7/71) received four vaccines, 6% (4/71) received three vaccines, and 2% (2/71) received two vaccines, simultaneously. Infants who did not receive all five vaccines simultaneously on a single day completed the indicated immunization the day after completion of the 3-day study period.

At the time of immunization, 44% of 239 study infants were in room air and receiving no medication; 29% were in room air but receiving xanthine or diuretics or were receiving O_2 by hood (FIO_2 0.22 to 0.30) with or without medication; and 27% were receiving FIO_2 >0.30, on CPAP, mechanical ventilation, or receiving corticosteroids with or without xanthine or diuretic therapy.

Fifty-two percent of infants did not have apnea, bradycardia, or O_2 desaturation episodes before or after immunization. Additionally, 32% had episodes of apnea, bradycardia, or O_2 desaturation before immunization, but the frequency of these episodes decreased or remained the same post-immunization. The remaining 16% (39/239) were considered to have immunization-associated cardiorespiratory events; 24 infants were asymptomatic before immunization but had episodes of apnea, bradycardia, or O_2 desaturation after immunization, and 15 infants who already had episodes of apnea, bradycardia, or O_2 desaturation before immunization had increase in the number of episodes after immunization. Twenty-six of 39 infants had initiation of O_2 therapy or increase in FIO_2. The remaining 13 of 39 infants had bag-mask ventilation, an initiation of CPAP or mechanical ventilation, or increase in ventilator settings. The onset of new cardiorespiratory symptoms or worsening cardiorespiratory status was noted 4 to 66 hours (mean ± SD of 25 ±15 hours; median of 21 hours) after immunization. Ninety-five percent (37/39) cardiorespiratory events occurred within 48 hours post-immunization. Table II shows the frequency of cardiorespiratory events with each single vaccine and with multiple separate vaccines simultaneously. Cardiorespiratory events were noted in 32% of those who received multiple vaccines. DTaP was associated with the highest incidence of cardiorespiratory events (χ^2 = 15.7, df = 4, P = .004) among groups given a single vaccine. HBV administration was not associated with cardiorespiratory events. Improvement or resolution of cardiorespiratory abnormalities was noted within 72 hours of onset of cardiorespiratory manifestation.

Twelve infants had a work-up for septicemia after immunization as directed by the attending physician. These infants had cardiorespiratory events for which intervention was positive pressure ventilation, and they also had elevated CRP values. However, blood cultures were negative and antibiotics were discontinued after 48 to 72 hours of treatment and without any further complication.

Following immunization, 40 % (95/239) of infants had nondetectable CRP (<0.7 mg/dL), 17% (41/239) had detectable CRP (0.7 to 1.6 mg/dL), and 43% (103/239) had ab-

Table II. CRP responses and cardiorespiratory events following immunization (n = 239)

Vaccines	CRP responses (mg/dL)			Cardiorespiratory events		
	Detectable	Abnormal	Highest level	Interventions		
Group	0.7 to 1.6	>1.6		Oxygen*	Ventilation†	Total
DTaP (n = 41)	14 (34%)	10 (24%)	12.1	6 (15%)	3 (7%)	9 (22%)
PVC7 (n = 26)	12 (46%)	14 (54%)	4.5	2 (8%)	1(4%)	3 (12%)
Hib (n = 27)	4 (15%)	19 (70%)	7.1	3 (11%)	0 (0%)	3 (11%)
IPV (n = 30)	3 (10%)	0 (0%)	1.1	1 (3%)	0 (0%)	1 (3%)
HBV (n = 44)	2 (5%)	0 (0%)	1.3	0 (0%)	0 (0%)	0 (0%)
Multiple (n = 71)	6 (8%)	60 (85%)	10.8	14 (20%)	9 (13%)	23 (32%)
Total (n = 239)	41 (17%)	103 (43%)		26 (11%)	13 (5%)	39 (16%)

*Initiation of oxygen supplementation or increase in FIO_2.
†Bag-mask ventilation, initiation or increase in mechanical ventilatory support such as continuous positive airway pressure (CPAP), or intermittent positive pressure ventilation (IPPV).

normal CRP (>1.6 mg/dL) values. Table II shows the elevated CRP values in the multiple and the single vaccine groups. Twenty-four percent (10/41) of infants who received DTaP had abnormal CRP. Immunization with HBV was not associated with abnormal CRP. Of infants with immunization-associated cardiorespiratory events, 85% (33/39) had abnormal CRP (>1.6 mg/dL). In six remaining infants, two in the DTaP group had detectable CRP (0.7 to 1.6 mg/dL), and three in the DTaP group and one in the IPV group had undetectable CRP (<0.7 mg/dL). No association was observed between the cardiorespiratory events and the magnitude of CRP responses.

To determine whether multiple vaccines or a single vaccine may be associated with abnormal CRP and cardiorespiratory events, a backward stepwise logistic regression model was used, controlling for the demographic and clinical variables listed in Table I. Variables significant at the .05 levels were retained in the model. Abnormal CRP values were associated with administration of multiple vaccines, (OR, 15.77; 95% CI 5.10-48.77) and the presence of IVH grades 3 or 4 (OR, 2.28; 95% CI 1.02-5.13). Cardiorespiratory events were related marginally to multiple vaccines (OR, 3.62; 95% CI 0.99-13.25) and significantly to GER (OR, 4.76; 95% CI 1.22-18.52). Compared with infants who received a single vaccine, infants who received multiple vaccines were almost four times more likely to have immunization-associated cardiorespiratory events and 16 times more likely to have abnormal CRP value (>1.6 mg/dL).

Because of our convenience sample, a post hoc power analysis was done. The power to detect differences between multiple vaccine and single vaccine groups for abnormal CRP was 1.00; for cardiorespiratory events, it was 0.98. The power for comparing each single vaccine against multiple vaccines for outcome of abnormal CRP was >0.80 for all except for Hib. However, the power for comparing any particular single vaccine against multiple vaccines for outcome of cardiorespiratory events was >0.80 for only IPV and HBV.

DISCUSSION

Our study revealed that some vaccines, including DTaP, even if administered alone were associated with cardiorespiratory adverse events and abnormal CRP values in premature infants in the NICU. However, the incidence of these events was higher following simultaneous administration of multiple vaccines compared with administration of a single vaccine. The AAP Committee on Infectious Diseases[21,22] reported on the absence of apnea in preterm infants receiving DTaP vaccine, based on the published experience by Schloesser et al.[14] The infants in this study[14] had higher BW and GA compared with ours, and they received immunization in outpatient clinics. More than 90% of infants in our study who were still in the NICU at 2 months of age had a history of chronic lung disease, were oxygen dependent, and/or were still receiving diuretic therapy. Because of their clinical status, our infants may have been more prone to develop respiratory events after immunization because of low respiratory reserve.[23]

Other investigators also have reported on cardiorespiratory events following immunization with DTaP-based multivalent vaccines[11-13] or when DTaP was given simultaneously with other vaccines.[10,15,16] Omenaca et al,[13] after excluding from their study infants with chronic illnesses and using only one lot of combination vaccine, observed cardiorespiratory events in 42% of infants with BW <1000 g. Also, Schulzke et al[12] studied only preterm infants with stable respiratory status and found a 13% incidence of apnea after immunization with DTaP-containing combination vaccines. Pfister et al[11] reported that 6% of preterm infants who received combination vaccines required bag-mask ventilation, and 19% had increased oxygen requirement. Ellison et al[16] reported a higher incidence of apnea with simultaneous administration of three vaccines compared with two vaccines (27% vs 9%). Slack et al[10] reported 38% incidence of cardiorespiratory events when infants were immunized simultaneously with DTaP-Hib and meningococcal vaccines. Goodman et al[15] reported increased frequency of apnea in preterm infants who had a history of AOP. These studies and ours suggest that cardiorespiratory events can occur with use of DTaP vaccine given alone, simultaneously with other vaccines, or as part of a combination vaccine.

The single vaccine injection as was used in this study is not the currently recommended approach. Combination vac-

cines are currently available and are preferred by the AAP. The combination vaccines with single injection may decrease the overall complications of vaccinations simultaneously or sequentially administered.

There are limited reports on CRP responses to immunization. CRP might increase after immunization because of the reactogenic effect of the vaccine with symptoms such as swelling and redness at the immunization site or fever. Also, CRP might increase after immunization because of immune activation.[24] Increased CRP has been observed in preterm infants following primary immunization with multiple vaccines that included DTwP[8,25,26] or DTaP.[16] CRP responses to individual vaccine have not been reported. In the present study, we observed abnormal CRP values in 24% to 70% of infants who received DTaP, PCV7, or Hib, individually, and in 85% of infants who received multiple vaccines simultaneously. CRP remained in the normal range in infants who received HBV and IPV vaccines.

A plausible explanation for variation in magnitude of CRP responses to immunization may be attributed to viral versus bacterial antigenic stimulation,[27] minor variability in the quantity of antigens in different vaccine lots, the multiple antigenic component of a vaccine, the presence and the quantity of aluminum adjuvant,[28] genetic polymorphism[29] or to decreased immunologic responses in some preterm infants.[22,30] Although there were more infants with diagnosis of AOP, GER, and IVH in the group receiving multiple vaccines, the additive effects of multiple vaccines or injections given simultaneously also may account for a higher incidence of abnormal CRP values and cardiorespiratory events.

Limitations of the study include absence of a control group and not having controlled for the vaccine lot. Moreover, not having masked nurses to vaccine(s) administered could have resulted in bias in reporting cardiorespiratory events, and in assessing the need for initiation of interventions. Additionally, this study did not have power to compare individual vaccines with multiple vaccines in relation to cardiorespiratory outcome. We also did not stratify for GA or for clinical conditions such as AOP, GER, or severe IVH when we randomized vaccine assignment, and we did not have measures of the infants' antibody responses to each vaccine for correlation with CRP changes.

In following the AAP guidelines[22] to initiate immunization of hospitalized premature infants at the postnatal age of 2 months, close monitoring of these infants for up to 48 hours would be needed because of the risk of cardiorespiratory events. These associated complications are more likely to occur with current practice of simultaneous administration of multiple vaccines. Also, contrary to previous reports,[21,22] cardiorespiratory events can be observed even if DTaP is given as a single vaccine. Administration of other vaccines given individually such as PVC7 and Hib also can be associated with cardiorespiratory events. A normal CRP before immunization suggests that cardiorespiratory events and abnormal CRP values following immunization are likely vaccination-associated.

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50 Years Ago in *The Journal of Pediatrics*

The social management of the epileptic child and his parents

Livingston S. J Pediatr 1957;51:137-45

Samuel Livingston's greatest legacy in pediatrics is perhaps his tireless promotion of the modern ketogenic diet, with its ratio of 4 grams of fat to 1 gram combined of carbohydrates and protein, as devised first by Wilder in 1921 for refractory epilepsy. However, many remember Livingston as a dedicated pediatric epileptologist at the Johns Hopkins Hospital before a neurology department ever existed there.

Fifty years ago, his clinical acumen was demonstrated in *The Journal* with a commentary to highlight the psychosocial management of the child with epilepsy. Despite scientific advances, Livingston's pearls remain timeless and should be reviewed.

- "Epilepsy is assigned to those patients who suffer with convulsions or seizures and in whom a defined cause cannot be established."
- "The parents must be reassured that nothing they have done or not done has contributed to the development of epilepsy."
- "Efforts should be directed toward raising a 'normal child.'"
- Children with epilepsy should be allowed to "participate in any of the activities usual for his age group."
- "We recommend only two major revisions for children who have seizures: (1) they should not be allowed to climb into positions from which a fall would be dangerous and (2) swimming should be supervised by adults."
- Only "if a patient suffers with frequent seizures or manifests side reactions . . . is it best that the school authorities be told about the condition in detail." For the child who has rare seizures not at school, not mentioning problems to the school will avoid stigma and misunderstanding.
- "There is no valid reason why a controlled epileptic who is physically and mentally capable of driving should be denied this privilege."
- "Outside the exotic vocations (air pilot, steeplejack, or a deep-sea diver) there is little that an epileptic cannot do."
- "Certainly there is no reason for the epileptic not to marry . . . The chances of an epileptic having an epileptic child varies all the way from 1:10 to 1:1000, the average being about 1:25."

Indeed, because the pediatrician has a long and trusted relationship with the child and family, Livingston's advice should be reinforced by today's primary physician. I would add only that intensive counseling is needed for the sexually active patient. Postpubertal girls requiring anticonvulsant medications should be started on oral folate 4 mg daily to minimize the risk of offspring with spina bifida, especially with carbamazepine, oxcarbazepine, or valproic acid, and offered less teratogenic alternatives. The family should also use resources such as the Epilepsy Foundation of America (*www.epilepsyfoundation.org*), the Epilepsy Therapy Development Project (*www.epilepsy.com*), or the International League Against Epilepsy (*www.ilae-epilepsy.org*).

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