

Risk of Seizures and Encephalopathy After Immunization With the Diphtheria-Tetanus-Pertussis Vaccine

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We evaluated the risks of seizures and other neurological events following diphtheria-tetanus-pertussis (DTP) immunization for 38 171 Tennessee Medicaid children who received 107 154 DTP immunizations in their first 3 years of life. There were 2 children with encephalitis; both had disease onset more than 2 weeks following DTP immunization. There were 277 children who had febrile seizures, 42 with afebrile seizures, and 37 with seizures associated with other acute neurological illness (acute symptomatic). The risk of febrile seizures in the 0 to 3 days following DTP immunization ($n = 6$) was 1.5 (95% confidence interval, 0.6 to 3.3) times that of the control period 30 or more days following DTP immunization. There was no evidence that in the 0 to 3 days following DTP immunization the risk of afebrile seizures ($n = 1$) or acute symptomatic seizures ($n = 0$) was increased. No child who was previously normal without a prior history of seizures had a seizure in the 0 to 3 days following immunization that marked the onset of either epilepsy or other neurological or developmental abnormality.

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NEUROLOGICAL events following in close temporal proximity to the administration of diphtheria-tetanus-pertussis (DTP) vaccine have repeatedly

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raised questions of a causal association.¹⁻³ However, there have been relatively few controlled studies that have

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evaluated the risks of febrile seizures, new-onset epilepsy, and the occurrence of other more severe permanent neurological illness following DTP administration. In a closely followed up cohort of children, seizures were reported within 48 hours of vaccine administration in 9 of 15 752 DTP immunizations; none of the children who developed seizures suffered any permanent neurological damage.^{4,5} Two controlled studies noted an excess of febrile seizures following DTP immunization; however, no association between DTP vaccine and epilepsy or other serious seizure disorder was found.^{6,7} The British National Encephalopathy Study estimated the rate of serious neurological disorders (that is, encephalopathy, unex-

plained coma, convulsions lasting >30 minutes or associated with persistent complications, infantile spasms, and Reye's syndrome) occurring within 7 days of DTP immunization in previously normal children to be 1 in 140 000 vaccinations^{8,9} and the rate of death or permanent brain damage to be about 1 in a third of a million doses.⁹ However, these estimates are based on small numbers of cases in the postimmunization period, and the interpretation of the study's authors is that these latter events may be attributable to DTP vaccine rarely if at all.⁹

We evaluated the risks of seizures and other neurological events following DTP immunization in 38 171 Tennessee children enrolled in Medicaid who received 107 154 DTP immunizations in their first 3 years of life. We studied this population because of the availability of both computerized immunization records and computerized diagnostic data. This predominantly poor, non-white population has not been well represented in prior controlled studies. Our objectives were to identify all seizures and acute encephalopathies in this population and to compare the rate of occurrence of these events in the immediate postimmunization period with the rate in the period 30 or more days following immunization.

METHODS

Sources of Data

The health department of each of the four most populous Tennessee counties

has a centralized, computerized record system for immunizations given through its public health clinic. These records were available for the years 1974 through 1984 for Shelby County, 1978 through 1984 for Davidson and Knox counties, and 1979 through 1984 for Hamilton County. Eighty-two percent of these immunization records were linked to Tennessee birth certificates for children born from 1974 through 1984.^{10,11} These computerized records were used to identify the time of DTP immunization of study children.

Medicaid reimburses medical services provided for qualifying poor in the United States.¹² An enrollment file identifies those persons eligible to receive Medicaid benefits with a unique Medicaid number and includes the dates of eligibility and the demographic characteristics of the enrollee. A computerized file of reimbursed bills for hospitalizations includes the dates of admission and up to two diagnoses (coded according to the *International Classification of Diseases, Version 8 [ICD-8]*) and two procedures. The outpatient file contains similar information for office, emergency department, and clinic visits. The pharmacy file consists of records of prescriptions filled at the pharmacy and identifies the date the prescription was filled and the drug and quantity dispensed. About 80% of children enrolled in Medicaid, and born in the study years, were also linked to birth certificates.¹⁰ Most of the remainder were likely to have been born out of state.

Definition of the Cohort

The study cohort consisted of children enrolled in the Tennessee Medicaid program in one of the four study counties within 90 days of birth who were linked to a Tennessee birth certificate with a birth date during the study years (county-specific as above) and who received at least one DTP immunization at county clinics or from Medicaid providers during those years on days 29 through 365 of life. The 38 171 study children constituted 29% of all children immunized in the public sector and 12% of all children born in the four study counties during the study years. Of children in the study cohort, 86% were non-white and 13% had a birth weight of less than 2500 g. By definition, all study children received at least one DTP immunization (the median age at first DTP immunization was 2 months), 95% had a second DTP immunization (median age, 5 months), 87% a third DTP immunization (median age, 8 months), and 67% a fourth DTP immunization (median age, 23 months).

Since cohort membership required at

least one DTP immunization, follow-up for each child began at the time of the first DTP immunization recorded in our data. Follow-up was restricted to the first 36 months of life since this period encompasses the time when most DTP immunizations are administered and the time of highest incidence of childhood seizures. Thus, follow-up ended at the first of the following dates: attainment of 36 months of age, loss of Medicaid eligibility, occurrence of an outcome of interest or a potential outcome of interest for which the record was not located, death, or the end of the study (December 31, 1984). The 38 171 cohort children had 60 562 years of follow-up (this represents 70% of the total follow-up time that would have been available if there was no loss of Medicaid eligibility), during which they received a total of 107 154 DTP immunizations. There were at least 30 days of follow-up in the study for 97% of these shots.

Identification of Neurological Events

The events of interest were the first nonneonatal seizure or episode of encephalopathy that resulted in a Medicaid reimbursement for a medical encounter between the first DTP immunization and the end of study follow-up. The classification of seizures was similar to that of Hauser and Kurland.¹³ *Neonatal seizures* were those occurring within the first 28 days of life. *Febrile seizures* were defined as seizures accompanied by fever and not considered to be symptomatic of an acute neurological illness; they were classified as *complex febrile seizures* if they lasted for more than 10 minutes or had focal features or if more than one seizure occurred within 24 hours. *Afebrile seizures* were those unaccompanied by fever or an acute neurological illness. *Symptomatic seizures* were those associated with acute neurological illness. *Encephalopathies* included acute or subacute encephalitis or encephalopathy of unknown cause, viral encephalitis, unexplained alterations of consciousness, and Reye's syndrome; encephalopathy could be associated with seizures as well. *Epilepsy* was defined as recurrent seizures, at least one of which was afebrile.

We identified potential outcomes of interest by screening Medicaid inpatient and outpatient claims with a wide variety of diagnosis codes.⁹ For diagnoses that seemed likely to identify a study event, both inpatient and outpatient claims were identified. These included encephalitis (*ICD-8* codes 65, 66, and 323), epilepsy (*ICD-8* codes 3312 and 345), symptoms referable to the nervous system (*ICD-8* codes 780 and

7801 through 7804), encephalopathy (*ICD-8* code 7817), and hallucinations (*ICD-8* code 7818). Several other less specific codes were used to identify potential cases only if the code occurred on an inpatient claim or on an outpatient claim that occurred within 30 days of a hospitalization. (The latter are denoted as inpatient associated.) These codes included specific viral encephalitis (*ICD-8* codes 54, 55, 56, and 72), unspecified hereditary and familial diseases of the nervous system (*ICD-8* code 3339), multiple sclerosis and other demyelinating diseases (*ICD-8* codes 340 and 341), other cerebral paralysis (*ICD-8* code 344), other diseases of the brain (*ICD-8* codes 3470 and 3479), syncope and collapse (*ICD-8* code 7825), transient paralysis of a limb (*ICD-8* code 7870), other ill-defined and unknown causes of morbidity and mortality (*ICD-8* code 796), other ill-defined conditions (*ICD-8* code 7960), postimmunization encephalitis (*ICD-8* code 9991), and complications in prophylaxis with vaccines (*ICD-8* codes E933 and E934). To identify seizures that did not receive any of the screening *ICD-8* codes, we also screened those children with a claim for an electroencephalogram and those who filled a prescription for an anticonvulsant (acetazolamide, carbamazepine, clonazepam, diazepam, ethosuximide, mephobarbital, methsuximide, paramethadione, phenobarbital, phenoximide, phenytoin, primidone, trimethadione, or valproic acid) within 7 days of a hospitalization.

Using the above screening criteria, potential outcomes of interest in 1187 study children were identified: 326 inpatient encounters, 203 inpatient-associated encounters, 526 outpatient encounters, 109 electroencephalograms, and 23 anticonvulsant prescriptions (categories are mutually exclusive). Records for all inpatient encounters were sought. For the outpatient and electroencephalogram encounters, only those records for which the provider was hospital based (emergency departments and hospital-based outpatient departments) were sought. Eight hundred twenty-eight (70%) records were available for review, including over 99% of inpatient encounters, 93% of inpatient-associated encounters, 41% of outpatient encounters, 69% of electroencephalograms, and 91% of anticonvulsants.

Records were abstracted using a structured protocol by a trained nurse who was unaware of the immunization status of the child unless it was stated in the medical record. Information on the first nonneonatal seizure or episode of encephalopathy that resulted in a medical encounter (index event) between the

first DTP immunization and the age of 36 months was abstracted and included date of onset of symptoms, presence of fever, type of seizure, prior history of seizures, preexisting neurological or developmental abnormality, number and type of subsequent seizures, and residual neurological or developmental abnormality in children who were previously normal.

Of the 1187 children with potential outcomes of interest, records were available for review for 828 (70%). Of these, 358 (43%) met our case definition and 470 (57%) were excluded. The cases consisted of 213 simple and 64 complex febrile seizures, 42 afebrile seizures (24 generalized motor, 11 focal motor, 3 infantile spasms, and 4 other or unknown type), 37 acute symptomatic seizures (13 associated with central nervous system infection, 12 with trauma, 6 with metabolic disorder, 3 with toxin, and 3 other), and 2 encephalopathies (1 viral encephalitis and 1 encephalitis of unknown type). The 470 exclusions consisted of 34 neonatal seizures only, 150 instances of a chronic preexisting neurological abnormality without seizures, 18 spells that were not clearly seizures, 82 diagnoses of failure to thrive, 121 other nonneurological events, and 65 miscoded records.

The 359 children for whom records were not reviewed are denoted as having potential seizures. Most of these children had non-hospital-based outpatient records only, which were not available to us. Based on the yield of the abstracted records by specific screening code, we estimated that 147 of these events would have met the case definition.

Statistical Analysis

Analyses were performed using both 5 and 10 age groups. Since the results did not differ, we present only the results using the 5 age groups: 29 to 180 days, 181 to 360 days, 361 to 540 days, 541 to 720 days, and 721 to 1080 days. Poisson regression analysis, a multivariate analysis for log-linear modeling of incidence rates,¹⁴ was used to estimate the relative risk of seizures after DTP immunization and to control for other potential confounding variables, including sex, race (white or nonwhite), county (Shelby, Davidson, Hamilton, or Knox), calendar years (1974 to 1977, 1978 to 1981, or 1982 to 1984), birth weight (<2500 g vs other), delayed first DTP immunization (>75th percentile for age [102 days] vs other), number of DTP immunizations (1 vs other), and number of days following DTP immunization (0 to 3, 4 to 7, 8 to 14, 15 to 29, or ≥30 days). Since the estimates obtained

Table 1.—Age-Specific Rates (per 1000 Person-Years) of Seizures in a Cohort of Tennessee Medicaid Children, 1974 Through 1984, With at Least One DTP Immunization*

Age, d	Person-Years	Febrile		Afebrile		Symptomatic		Potential Seizures	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
29-180	9257	30	3.2	7	0.8	7	0.8	52	5.6
181-360	14 667	72	4.9	14	1.0	7	0.5	105	7.2
361-540	12 105	76	6.3	8	0.7	9	0.7	85	7.0
541-720	9838	55	5.6	6	0.6	5	0.5	54	5.5
721-1080	14 694	44	3.0	7	0.5	9	0.6	63	4.3
Total	60 562†	277	4.6	42	0.7	37	0.6	359	5.9

*DTP indicates diphtheria-tetanus-pertussis.

†Numbers do not total to 60 562 because of rounding.

Table 2.—Characteristics of Seizures in a Cohort of Tennessee Medicaid Children, 1974 Through 1984, With at Least One DTP Immunization*

Seizure Type	No.	% Prior Neurological/Developmental Abnormality	% Prior Seizure	% Epilepsy
Complex febrile	64	6.3	3.1	4.7
Simple febrile	213	2.3	10.8	0.9
Afebrile	42	14.3	40.5	61.9
Symptomatic	37	16.2	10.8	16.2

*DTP indicates diphtheria-tetanus-pertussis.

from this model did not differ materially from those obtained from a simpler model that controlled only for age, only the latter are presented. The GLIM software¹⁵ was used for all analyses.

RESULTS

In this population of 38 171 Medicaid children, 356 children (0.9%) had a medical encounter for a seizure and 2 children were hospitalized with encephalopathy between their first DTP immunization and 36 months of age. The 2 children with encephalopathy both had their onset of illness more than 2 weeks following DTP immunization, and neither had permanent sequelae. These 2 children will not be considered further. An additional 359 children had screening codes that were consistent with a possible seizure, but there was no confirmation by chart review. These were analyzed separately as potential seizures (see the "Methods" section).

Table 1 shows the age-specific incidence of seizures and potential seizures for the study cohort. The rate of febrile seizures increased with age and peaked at 6.3 seizures per 1000 person-years between 12 and 18 months of life. The rate of afebrile seizures was slightly higher in the first year of life, peaking at 1 seizure per 1000 person-years, and declined slowly thereafter. Acute symptomatic seizures ranged from 0.5 to 0.8 per 1000 person-years. Potential cases followed a pattern similar to that of the febrile seizures.

Sixty-four (23%) of the febrile seizures had complex features (Table 2). Children with complex febrile seizures were more likely than those with simple febrile seizures both to have a history of prior neurological or developmental abnormality (6.3% and 2.3%, respectively) and to develop epilepsy (4.7% and 0.9%). A prior neonatal seizure or another prior seizure that did not result in a medical encounter was reported in 3.1% of those with complex febrile and 10.8% of those with simple febrile seizures. Of those with afebrile seizures, 14.3% had a prior neurological or developmental abnormality noted, 40.5% had prior seizures, and 61.9% developed epilepsy. Of those with acute symptomatic seizures, 16.2% had prior neurological or developmental abnormalities, 10.8% had prior seizures, and 16.2% developed epilepsy.

There were six febrile seizures in the 0 to 3 days following immunization (Table 3). The risk of febrile seizures in this interval was 1.5 (95% confidence interval, 0.6 to 3.3) times that of the period 30 or more days following DTP immunization. When this analysis was restricted to febrile seizures in children with no prior history of seizure (n = 252), there were five febrile seizures in the 0 to 3 days following DTP immunization, yielding a relative risk of 1.3 (95% confidence interval, 0.5 to 3.3). Other events in the 0- to 3-day interval following DTP immunization included one afebrile seizure, zero symptomatic seizures, and

Table 3.—Relative Risk of Seizures According to Interval After DTP Immunization in a Cohort of Tennessee Medicaid Children, 1974 Through 1984*

Seizure Type	0-3 d		4-7 d		8-14 d		15-29 d		30+ d	
	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (Reference)
Febrile	6	1.5 (0.6-3.3)	4	0.9 (0.3-2.3)	6	0.7 (0.3-1.7)	19	1.1 (0.7-1.8)	242	1
Afebrile	1	1.3 (0.2-9.7)	2	2.2 (0.5-9.9)	1	0.6 (0.1-4.9)	3	0.9 (0.3-3.1)	35	1
Symptomatic	0	0.0 . . .	0	0.0 . . .	0	0.0 . . .	4	1.3 (0.4-3.9)	33	1
Potential	6	1.0 (0.5-2.3)	5	0.7 (0.3-1.8)	11	0.9 (0.5-1.7)	36	1.4 (1.0-2.1)	301	1

*Estimates were obtained with use of the Poisson regression model, controlling for age group. DTP indicates diphtheria-tetanus-pertussis; RR, relative risk; and CI, confidence interval.

six potential seizures, with no evidence for an increased rate of occurrence compared with the control period of 30 or more days following DTP immunization. The risks of febrile seizures in the 0- to 7-day and 0- to 29-day intervals were 1.1 (95% confidence interval, 0.6 to 2.2) and 1.0 (95% confidence interval, 0.7 to 1.5), respectively. The corresponding risks for afebrile seizures were 1.8 (95% confidence interval, 0.5 to 6.3) and 1.1 (95% confidence interval, 0.4 to 2.6), respectively.

Four children who were previously normal and had no prior seizures developed some neurological or developmental abnormality following the index seizure. In only 1 was the index event a febrile seizure, and this occurred more than 30 days following immunization. The other 3 occurred after acute symptomatic seizures. An additional 11 children who were previously normal developed epilepsy. One of these children had an initial afebrile seizure in the 8 to 14 days following DTP immunization; the initial seizures for the other 10 were all in the period 30 or more days after immunization.

COMMENT

Following DTP immunization, temperature of 38°C or greater has been reported within 48 hours in 47% of children.⁴ It is in this early postimmunization period that adverse effects thought to be associated with immunization are usually reported.^{1,3} In this population of 38 171 Tennessee Medicaid children who received 107 154 DTP immunizations in their first 3 years of life, no child had the onset of encephalopathy, epilepsy, or other serious neurological disease in the first week following DTP immunization. Indeed, there was no significant increase in febrile, afebrile, or acute symptomatic seizures in the early postimmunization period, compared with the control period of 30 or more days following DTP immunization.

Our finding of no significantly increased risk following DTP immunization of febrile seizures that generated a medical encounter has not been consistently

seen in other studies. When analyzing febrile seizures that resulted in a hospitalization or pharmacologic treatment, Walker et al⁶ reported an incidence in the immediate postimmunization period that was 3.7 times (95% confidence interval, 1.4 to 10) that in the period 30 days or more after immunization. The age distribution of febrile seizures in Denmark was found to correlate significantly with the timing of immunization.⁷ A peak in febrile seizures changed from age 15 months to age 10 months corresponding to the change in age of scheduled immunization. A similar shift in timing of febrile seizures was not observed with the simultaneous change in pertussis immunization from the age of 4 to 8 months to the age of 1 to 3 months. On the other hand, Pollock and Morris¹⁶ found the rate of seizures in children 9 to 24 months of age without a personal or family history of seizures to be 5.3 and 5.6 per 10 000 in the 28 days following DTP and diphtheria-tetanus immunization, respectively, and almost identical to the background rate of 5.2 per 10 000.

Given the high incidence of fever following DTP immunization, one might expect an increase in febrile seizures in the immediate postimmunization period. Why, then, have study results differed? One reason may be the low precision of the estimates of the risk of febrile seizures in the immediate postimmunization period. The power of our study to detect an increased risk during this time was reduced by three factors. First, we had limited person-time following DTP immunization for children 9 to 24 months of age, the ages at which one would expect the risk of febrile seizures related to DTP immunization to be highest.¹⁷ Second, the use of antipyretics following DTP immunization, for which we have no information, may have further reduced the numbers of children at risk. Finally, it is possible that some of the highest-risk children (eg, those with a personal or family history of seizures) were not immunized and thus were excluded from our study population. Thus, the 95% confidence interval for our esti-

mate of relative risk in the period 0 to 3 days following DTP immunization, 0.6 to 3.3, is broad and substantially overlaps that of 1.4 to 10.0 from the recent study of Walker et al.⁶

Another potential problem is the completeness of reporting of the less serious neurological events. Our study was confined to seizures followed by a hospitalization or treatment in a hospital outpatient department. There were 359 children who were identified as possible cases but whose records were not reviewed, primarily because we did not seek non-hospital-based outpatient records. To assess whether this exclusion resulted in underestimation of the risk of neurological events following DTP immunization, we performed a separate analysis of these potential, but unconfirmed, cases. We noted no clustering of events in this group following immunization. However, the yield of the other outpatient screening codes suggests that fewer than 50% of these encounters were for a seizure that met our case definition; this misclassification would reduce the power of this analysis to detect an effect of DTP immunization. However, exclusion of these children should not bias our results unless they were different from other cases in respect to the timing of their events in relation to immunization.

Walker et al⁶ limited their study to seizures that resulted in hospitalization or pharmacologic treatment, and that of Pollock and Morris¹⁶ was limited to those that resulted in a hospitalization. Rates of seizures in these studies and in our study are lower, therefore, than those reported from the National Institute of Neurological and Communicative Disorders and Stroke Collaborative Perinatal Project cohort study of 52 360 children followed up from birth to 7 years, in which seizures were ascertained from regular parent interviews supplemented by medical records.¹⁸ The rates of febrile seizures in the first and second 6 months of life in that study were 4.4 and 14.4 per 1000 compared with rates in our population of 3.2 and 4.9 per 1000. Thus, differences among these studies in the

estimated risk of febrile seizures following DTP immunization may result from both the differences in the methods of case ascertainment and differences among the populations studied in the likelihood of seeking medical attention for a less serious, self-limited neurological event such as a febrile seizure. This provides further reason to view with caution our finding of no significant increase in the risk of febrile seizures following DTP immunization.

However, there is a greater concordance among studies as to whether the risk of serious neurological disorders that are likely to receive medical attention is increased following DTP immunization. We found no encephalopathies in the 14 days following DTP immunization and no increase in the risk of afebrile seizures. This is consistent both with no risk and with the estimate from the British National Childhood Enceph-

alopathy Study of one new serious neurological event attributable to DTP immunization per 110 000 vaccinations.⁸ In a controlled cohort of study children who received 106 000 doses of DTP vaccine, Walker et al⁶ found no cases of unexplained encephalopathy in close proximity to vaccination and no significant increase in serious seizure disorders in the 0- to 3-day interval following immunization. Pollock and Morris¹⁶ found relatively large differences in neurological events that occurred within 28 days of DTP immunization compared with diphtheria-tetanus immunization when they used a voluntary reporting system, but no differences in the rate of neurological events that resulted in hospitalization when hospital records were systematically screened. Investigators reported no change in the age at onset of epilepsy or infantile spasms in Denmark that was associated

with a change in the age at pertussis immunization there, suggesting a lack of relationship between pertussis immunization and these neurological events.⁷ Therefore, our negative finding in a population of predominantly nonwhite, low-income children immunized in the public sector reinforces the findings of previous investigators working in other populations^{6,8,16} that serious neurological events are rarely, if ever, caused by DTP immunization.

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