

THE RISK OF SEIZURES AFTER RECEIPT OF WHOLE-CELL PERTUSSIS OR MEASLES, MUMPS, AND RUBELLA VACCINE

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ABSTRACT

Background The administration of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with seizures. We studied the relation between these vaccinations and the risk of a first seizure, subsequent seizures, and neurodevelopmental disability in children.

Methods This cohort study was conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures. We calculated the relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities.

Results Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42). Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). Neither vaccination was associated with an increased risk of nonfebrile seizures. The number of febrile seizures attributable to the administration of DTP and MMR vaccines was estimated to be 6 to 9 and 25 to 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities.

Conclusions There are significantly elevated risks of febrile seizures after receipt of DTP vaccine or MMR vaccine, but these risks do not appear to be associated with any long-term, adverse consequences. (N Engl J Med 2001;345:656-61.)

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VACCINATION against pertussis was first linked to adverse neurologic events in 1933.¹ One study found that vaccination with diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine was associated with an elevated risk of seizures and encephalopathy (relative risk, 3.3; 95 percent confidence interval, 1.4 to 8.2).² In another study, receipt of DTP vaccine was

associated with an increased risk of febrile seizures within three days after vaccination (relative risk, 3.7; 95 percent confidence interval, 1.4 to 10.0), but not of nonfebrile seizures.³ However, two other studies found no significant increase in the risk of febrile or nonfebrile seizures after immunization with DTP vaccine.^{4,5} A meta-analysis of these studies estimated that receipt of DTP vaccine was associated with a relative risk of febrile seizures of 1.8 (95 percent confidence interval, 1.2 to 2.7) but was not associated with an increased risk of nonfebrile seizures.⁶ Subsequently, Farrington et al. found that the risk of febrile seizures was elevated during the first three days after the administration of DTP vaccine (relative risk, 3.0; 95 percent confidence interval, 1.6 to 5.5), though only in association with the third dose of vaccine.⁷

The relation between the measles, mumps, and rubella (MMR) vaccine and seizures has been less well studied. Griffin et al. reported that immunization with MMR vaccine increased the risk of febrile seizures during the first 7 to 14 days after vaccination (relative risk, 2.1; 95 percent confidence interval, 0.7 to 6.4),⁸ and Farrington et al. found that the risk was increased during the first 6 to 11 days after vaccination (relative risk, 1.51; 95 percent confidence interval, 1.21 to 1.90).⁷ These findings are consistent with the timing of the onset of fever after vaccination with live attenuated measles virus.

In 1991 the Centers for Disease Control and Pre-

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vention initiated the Vaccine Safety Datalink project, a population-based study of adverse events after childhood immunization in four large regional health maintenance organizations (HMOs).⁹ This large cohort allows the study of associations between vaccinations and rare adverse outcomes, ongoing surveillance of new syndromes or diseases hypothesized as due to vaccination, and the study of newly introduced vaccines, combinations of vaccines, and schedules of vaccination.

We used this cohort to delineate in more detail the relation between the DTP and MMR vaccines and first-time seizures, as well as the outcomes among children with seizures. Because the abstraction of medical records is time consuming and expensive, we also evaluated the usefulness and validity of automated data as a surveillance tool.

METHODS

Study Sites, Sources of Data, and Identification and Classification of Cases

The design of the Vaccine Safety Datalink project has been described in detail previously.⁹ Data are collected from four HMOs — the Group Health Cooperative in Seattle; Northwest Kaiser Permanente in Portland, Oregon; Kaiser Permanente of Northern California in Oakland; and Southern California Kaiser Permanente in Torrance — with an annual birth cohort of approximately 90,000. More than 600,000 children under the age of seven years are enrolled at any point in time, or about 1 of every 40 young children in the United States. Children entered the cohort at birth, on the date of their enrollment in the HMO, or at the beginning of a study site's observation period, whichever came last, and remained in the cohort until the age of seven years, disenrollment from the HMO, or the end of the observation period, whichever occurred first.

Potential seizures were identified through the automated data systems of each HMO, on the basis of visits classified according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), as code 333.2 (myoclonus), code 345 (epilepsy), code 779.0 (convulsions in a newborn), or code 780.3 (convulsions). All four HMOs had data bases that automatically entered diagnostic information on hospitalizations, and all except Southern California Kaiser Permanente had automated entry of data obtained from visits to the emergency department and for urgent care. Outpatient data were available from all 23 Group Health Cooperative clinics and from 3 of the 27 Kaiser Permanente of Northern California clinics. At Northwest Kaiser Permanente, additional potential cases of seizure were identified with the use of computerized data on anticonvulsant medications, referrals to neurology clinics, and electroencephalographic records. Consequently, the identification of all cases of seizure at the HMOs was not complete, but all seizures leading to hospitalization and most leading to emergency or urgent care visits were identified.

Two HMOs, the Group Health Cooperative and Northwest Kaiser Permanente, abstracted the medical records of all children with a possible seizure to validate and classify seizure diagnoses and to collect additional information. To expedite chart review, the other two, larger HMOs reviewed only a sample of potential cases. At Kaiser Permanente of Northern California, all cases of seizure that occurred within 30 days after immunization and a random sample of 20 percent of cases of seizure in children who had not been vaccinated within the 30 preceding days were reviewed. At Southern California Kaiser Permanente, 26 percent of cases of seizure were randomly selected for review without regard to vaccination status. Experienced medical-record abstractors reviewed the charts using standardized chart-abstraction forms and instructions, with the final disposition of each case determined by physician investigators.

Chart-reviewed episodes of seizure were classified according to criteria similar to those of Griffin et al.⁴ and Gale et al.⁵ Simple febrile seizures were defined as short, generalized seizures, accompanied by documented fever or a parental report of fever. Complex febrile seizures were defined as febrile seizures that occurred more than once in 24 hours and either lasted for at least 12 minutes or were accompanied by focal signs. Nonfebrile seizures were defined as seizures that were unassociated with fever and not attributable to an existing disease process. In this latter group, we also included seizures among children with a diagnosis of epilepsy or residual seizure disorder. Seizures that were due to an underlying disease process such as infection or trauma were excluded from analysis. The analysis of the risk of vaccination included only the first episode of seizure in each child, as confirmed by review of the medical records.

Data on Immunization

Data on immunization were derived from automated immunization-tracking systems initially developed to collect information on all routinely administered immunizations.⁹⁻¹² The data in the tracking systems undergo extensive quality review and show high rates of agreement with data obtained from chart reviews.¹³

Statistical Analysis

We used stratified Cox proportional-hazards analysis to assess the association between immunization and the occurrence of a first seizure. Calendar time was used as the time variable, with stratification according to age (± 1 day) and HMO. Each child with a seizure was therefore compared with other children who were members of the same HMO on the day of the onset of the seizure and who were born within one day of the child with a seizure. The intervals used to assess exposure to DTP or MMR vaccine were based on the number of days since exposure: the day of vaccination and 1 to 7, 8 to 14, and 15 to 30 days after vaccination. The reference group at the time of the seizure was composed of children matched for age, calendar time, and HMO but who had not had a vaccination in the preceding 30 days. We assessed the risk of nonfebrile seizures 0 to 7, 8 to 14, and 15 to 30 days after vaccination, since no seizures were recorded on the same day as vaccination. To adjust for the sampling of cases in the Kaiser Permanente of Northern California and Southern California Kaiser Permanente populations, observations were weighted inversely according to the probability of being sampled.^{14,15} For example, a child with seizures who had been vaccinated at Kaiser Permanente of Northern California would be assigned a weight of 1.0, but a child with seizures who had not been vaccinated would be assigned a weight of 5.0, since the random sample consisted of 20 percent of the population.

The calculations of the risk attributable to vaccination were carried out with the use of standard methods. We used the background rate of febrile seizures during the first two years of life to calculate the risk attributable to immunization with DTP vaccine, but we used the background rate for the second year of life to calculate the risk attributable to MMR vaccine. Because these calculations are dependent on the correct ascertainment of the background rates of seizures, we used two different sources of data and present both results. First, we used data from the Group Health Cooperative to provide information on the background rates of seizure, because at this site there was complete ascertainment of seizures. Second, we used published data from a cohort study of 18,500 children in Oakland, California.¹⁶

Follow-up Study

To assess outcomes among children with febrile seizures, we categorized children as exposed if the seizure followed immunization with DTP vaccine within 7 days or MMR vaccine within 7 to 21 days. These intervals (which differed slightly from those used in the analysis of seizures after vaccination) were chosen on the basis of the risk intervals from past studies⁶ and on the onset and duration of fever after the receipt of MMR vaccine. In the follow-

up study, unlike the risk study, we included children whose first febrile seizure preceded the development of the automated tracking system for vaccines, since vaccination history was available in the medical record. Children with febrile seizures at other times were categorized as unexposed. Children with nonfebrile seizures were not studied, since there is no apparent association between such seizures and immunization with DTP or MMR vaccine. Follow-up data on subsequent seizures were available from the medical record. Data on neurobehavioral disorders were obtained from automated outpatient data at two sites: the Group Health Cooperative, from March 1991 through December 1996, and Kaiser Permanente of Northern California, from March 1991 through March 1998.

The ICD-9-CM diagnoses assessed included attention-deficit disorder (code 314.0), learning disorders (codes 315.0 to 315.9), mental retardation (codes 317 to 319), other speech disturbances (code 784.5), emotional disturbance (code 313), personality disorder (code 301), repetitive-movement disorder (code 307.3), obsessive-compulsive disorder (code 300.3), infantile autism (code 299.0), childhood type of schizophrenia (code 299.9), and other psychoses of early childhood (code 299.8). The specificity of these diagnoses has been found to be high in previous investigations, ranging from 75 percent for speech disorders to 83 percent for autism, although 69 percent of the cases of attention-deficit disorder had been diagnosed by the primary care physician alone.

RESULTS

Figure 1 shows the period of data collection and the number of children at each site, the number of person-years of observation, and the number of vaccinations with DTP and MMR vaccines. Using the automated data, we identified 2281 possible first seizures. Using the random-sampling plan previously described, we selected a total of 1094 children for chart review. Among these children, 716 were confirmed to have had a first seizure during the study period. The primary reason for nonconfirmation was the identification of an earlier seizure. First seizures were classified as follows: 487 febrile seizures (460 simple and 27 complex), 137 nonfebrile seizures, 36 infantile spasms or neonatal seizures, and 56 seizures due to other causes (e.g., infection or injury). Among the febrile seizures, 42 occurred within 30 days after the receipt of DTP vaccine and 32 within 30 days after the receipt of MMR vaccine. Among the nonfebrile seizures,

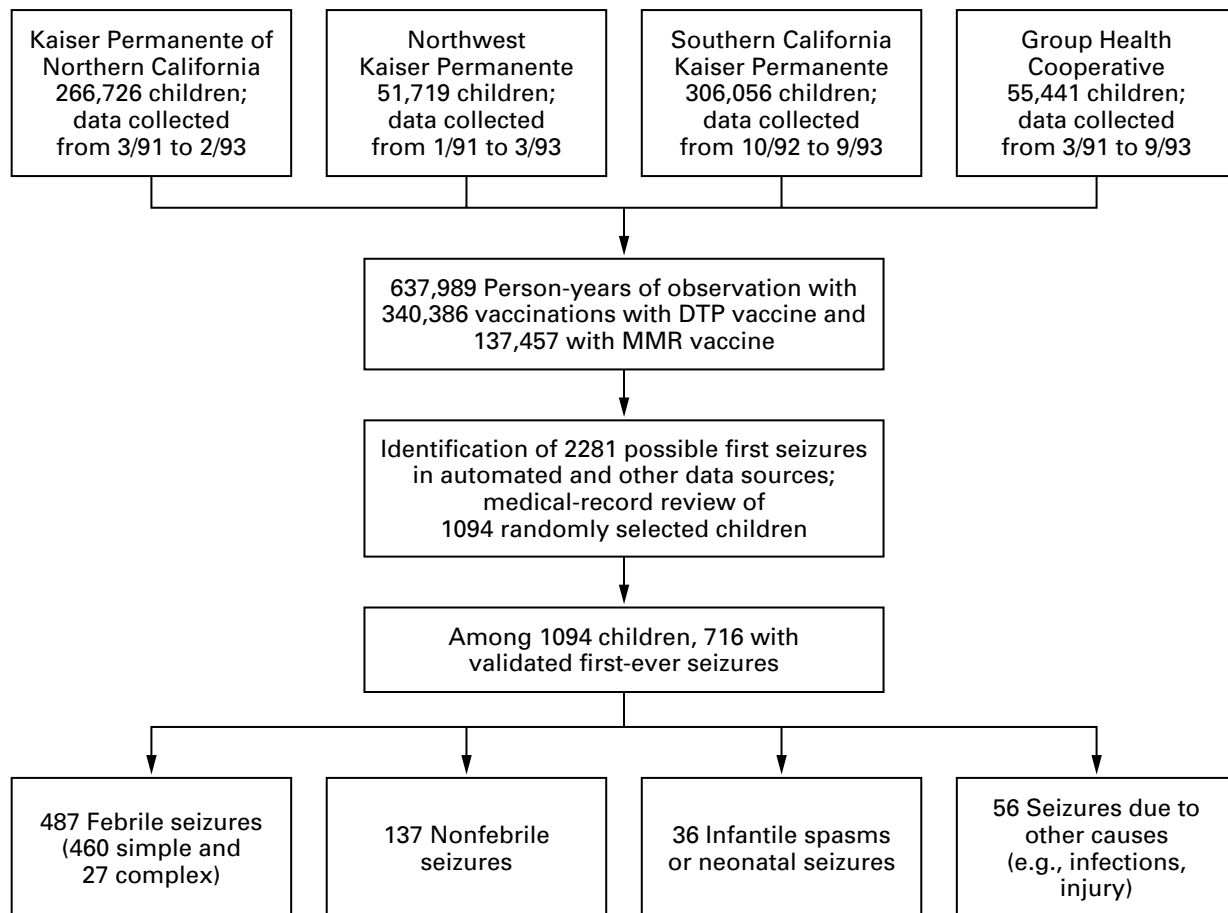


Figure 1. Collection and Validation of Data on Seizures at the Four Health Maintenance Organizations.

The process of validation is described in the Methods section. Most nonvalidated episodes of seizure were recurrent rather than initial episodes. DTP denotes diphtheria and tetanus toxoids and whole-cell pertussis, and MMR measles, mumps, and rubella.

10 occurred within 30 days after the receipt of DTP vaccine and 3 within 30 days after the receipt of MMR vaccine. Five of the febrile seizures were verified as occurring on the same day the DTP vaccine was given. No febrile seizures occurred on the same day the MMR vaccine was given, and no nonfebrile seizures occurred on the day the DTP or MMR vaccine was given.

Relative Risks of Seizure after Vaccination

Vaccination with DTP vaccine was associated with an elevated risk of febrile seizures on the day of administration (relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42), after adjustment for age, sex, HMO, calendar time, and receipt of MMR vaccine (Table 1). This risk did not persist and was not significantly elevated above base line 1 to 7 days, 8 to 14 days, or 15 to 30 days after vaccination. Among infants 0 to 12 months old, the relative risk of seizures on the day of vaccination with DTP vaccine was 9.27 (95 percent confidence interval, 1.21 to 70.78), whereas the relative risk was 3.06 (95 percent confidence interval, 0.67 to 13.96) among children 13 to 24 months old. This difference in relative risk was not statistically significant when tested with an interaction term for exposure and age. The sample size did not permit the assessment of whether the relative risk associated with the concomitant administration of DTP vaccine and MMR vaccine differed from that associated with the administration of each vaccine separately during the second year of life.

After adjustment for age, sex, HMO, calendar time, and receipt of DTP vaccine, the administration of MMR vaccine was associated with a relative risk of febrile seizures of 2.83 from 8 to 14 days after vaccination (95 percent confidence interval, 1.44 to 5.55), but it was not associated with an elevated risk 0 to 7 days or 15 to 30 days after vaccination. Neither the administration of DTP vaccine nor the administration of MMR vaccine was associated with significantly elevated risks of nonfebrile seizures at any time after vaccination (Table 1).

Risks of Seizures Attributable to Vaccination

Using the background rates of seizure in the Group Health Cooperative, we found that there were 5.6 and 25.0 additional febrile seizures per 100,000 children receiving DTP and MMR vaccines, respectively. Using published background rates of seizure from Kaiser Permanente of Northern California, we found that there were 8.9 and 34.2 additional febrile seizures per 100,000 children immunized with DTP and MMR vaccines, respectively.¹⁶ For these calculations, we used the estimated relative risks in Table 1 for each period of exposure, since these are the best estimates.

Analysis of Automated Information on Outcome

We analyzed the automated data using episodes of seizure identified through the automated data system

TABLE 1. ASSOCIATION BETWEEN THE ADMINISTRATION OF DTP OR MMR VACCINE AND A FIRST SEIZURE.*

TIME SINCE VACCINATION	ADMINISTRATION OF DTP VACCINE		ADMINISTRATION OF MMR VACCINE	
	NO. OF EVENTS	RELATIVE RISK (95% CI)	NO. OF EVENTS	RELATIVE RISK (95% CI)
Febrile seizures				
Same day	5	5.70 (1.98–16.42)	0	—
1–7 days	9	1.16 (0.53–2.56)	8	1.73 (0.72–4.15)
8–14 days	10	1.12 (0.53–2.33)	13	2.83 (1.44–5.55)
15–30 days	18	1.43 (0.82–2.50)	11	0.97 (0.49–1.95)
Nonfebrile seizures				
0–7 days	4	1.94 (0.62–6.12)	1	—
8–14 days	2	0.77 (0.16–3.67)	1	1.11 (0.11–11.28)
15–30 days	4	1.05 (0.32–3.37)	1	0.48 (0.05–4.64)

*For each analysis, values were adjusted for age, sex, health maintenance organization, calendar time, and the administration of the other vaccine. CI denotes confidence interval.

of each of the four HMOs. For this analysis, we used all 2281 possible first seizures identified in the computerized records and did not use information derived from the review of medical records. Therefore, febrile seizures could not be distinguished from nonfebrile seizures, and recurrent or nonvalidated seizures may have been included. Nonetheless, receipt of DTP vaccine was associated with an elevated risk of seizures on the day of vaccination (relative risk, 3.62; 95 percent confidence interval, 2.08 to 6.31), and receipt of MMR vaccine was associated with an increased risk 4 to 7 days after vaccination (relative risk, 1.77; 95 percent confidence interval, 1.03 to 3.02) and 8 to 14 days after vaccination (relative risk, 2.68; 95 percent confidence interval, 1.84 to 3.90).

Follow-up Study

A total of 41 children had febrile seizures soon after vaccination (18 soon after the receipt of DTP vaccine only, 22 after the receipt of MMR vaccine only, and 1 after the receipt of both DTP and MMR vaccines), and 521 children had febrile seizures in the absence of vaccination. These numbers are higher than in the risk analysis, since we included all first febrile seizures identified, not just those within the periods indicated in Figure 1. Children who had a febrile seizure after the receipt of DTP or MMR vaccine were no more likely to have a subsequent seizure than children who had febrile seizures in the absence of vaccination (relative risk, 0.65; 95 percent confidence interval, 0.32 to 1.35). None of the children with febrile seizures after vaccination had subsequent nonfebrile seizures or were given a diagnosis of epilepsy. Among the children who had febrile seizures in the absence of vaccination, 1.5 percent of those who were followed for six months were given a diagnosis of epilepsy, as

were 2.7 percent of those followed for one year and 5 percent of those followed for two years.

A total of 273 children with febrile seizures at Kaiser Permanente of Northern California and the Group Health Cooperative were followed for neurobehavioral disorders. In the case of 25 children one or more learning or developmental disabilities were diagnosed, including speech and language disorders in 15, attention-deficit disorder in 10, developmental delay in 7, and other learning disorders in 2. The average age at diagnosis was 4.3 years (range, 10 months to 12.5 years). The risk of one of these conditions did not differ between children who had been exposed and those who had not been exposed, after adjustment for age at the time of the first febrile seizure (relative risk, 0.56; 95 percent confidence interval, 0.07 to 4.2).

DISCUSSION

We found significantly elevated risks of febrile seizures on the day of the administration of DTP vaccine and 8 to 14 days after the administration of MMR vaccine. We did not find a significantly elevated risk of febrile seizures at any other time after vaccination, nor did we find an elevated risk of nonfebrile seizures at any time after vaccination with DTP or MMR vaccine. This risk translates into approximately 6 to 9 additional febrile seizures attributable to DTP vaccine for every 100,000 children who are vaccinated and 25 to 34 additional febrile seizures attributable to MMR vaccine. The number of febrile seizures attributable to vaccination did not vary substantially whether we performed these calculations using our own data on background rates of febrile seizures or those from other studies.¹⁶ Our results are consistent with those of Farrington et al., who estimated that approximately 6 and 33 febrile seizures were attributable to vaccination after 100,000 doses of DTP vaccine and MMR vaccine, respectively.⁷

Our findings of elevated rates of febrile seizures after the administration of DTP and MMR vaccines are consistent with those of earlier reports.²⁻⁸ Although the results of some of these studies did not reach statistical significance, our large study had more power to detect a positive association. Our follow-up analysis of children with febrile seizures after vaccination indicates that they are at no greater risk of subsequent seizures, epilepsy, or neurodevelopmental disorders than are children who have febrile seizures in the absence of vaccination. Our conclusions are limited by the relatively small number of children with seizures who received the vaccines, although the upper limit of our 95 percent confidence interval for the risk of subsequent seizures was low (1.35), suggesting that we did not miss a true risk larger than this. In the case of neurodevelopmental disabilities, the upper limit of the 95 percent confidence interval was 4.2, suggesting that we could have missed a moderate association of lesser magnitude. It would not be appropriate to com-

pare children who had febrile seizures with children who had never had a febrile seizure, since the former group may have a higher risk of febrile seizure that is unrelated to vaccination.

One limitation of our study was the difference in the methods of case ascertainment among the HMOs. This variation probably led to the preferential identification of children with more severe or serious episodes of seizure, but it would not necessarily bias the association between vaccination and seizure. A second limitation concerned the misclassification of vaccination status, since data from medical records and automated data on vaccination do not always agree.¹³ Using only automated data on vaccination status, as we did, may have led to slight underascertainment of the number of children who had been vaccinated, and this nonspecific misclassification would tend to decrease the relative risk slightly. Finally, disenrollment from the HMO limits further observation. However, only 13.7 percent of children were disenrolled during the study period, and this percentage was lower among those who had seizures (12.1 percent) than among those who did not (13.7 percent).

Since the period covered by this study, the use of acellular pertussis (DTaP) vaccine has largely replaced the use of whole-cell pertussis (DTP) vaccine in the United States, although DTP vaccine is still commonly used worldwide.^{17,18} Both vaccines are cost effective.¹⁹

A transient increase in the risk of febrile seizures should not obscure the benefits of vaccination with the DTP and MMR vaccines.²⁰ Vaccination has reduced childhood morbidity and mortality resulting from diseases such as smallpox, poliomyelitis, and invasive infection with *Haemophilus influenzae* type b.²⁰ Vaccination with DTP and MMR vaccines has also reduced the incidence of neurologic disabilities that would have resulted from pertussis or measles.²¹⁻²³ Given these benefits, it is reassuring that vaccination with DTP and MMR vaccines does not appear to increase the risk of nonfebrile seizures or long-term neurodevelopmental problems among children who have febrile seizures after vaccination. Two large, population-based studies have found that children with febrile seizures do not appear to differ from children without febrile seizures in terms of intelligence, behavior, and academic progress.^{24,25} Our study provides additional evidence that children who have vaccine-associated febrile seizures are at no greater risk for epilepsy or learning, behavioral, or psychiatric disorders than other children with febrile seizures.

An important finding from our study is that the results of the analysis of automated data on outcomes and vaccination from the Vaccine Safety Datalink project showed remarkably good concordance with the analysis of cases validated by an extensive review of medical records. We believe that future analyses using automated data on outcomes and exposure from HMOs that are routinely collected for the Vaccine

Safety Datalink project will be informative and can be used in lieu of information obtained by additional time-consuming and expensive studies. Repeated analyses of these linked data bases will be important in the future, in view of the rapidly changing schedule of childhood vaccinations, which now includes vaccines such as the DTaP, varicella, and pneumococcal vaccines.^{26,27} Use of the automated system will allow initial rapid assessment of the risk of seizure if concern should arise about a new vaccine or combination of vaccines, without the need to rely solely on reviews of medical records.

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