Risk of Febrile Seizures and Epilepsy After Vaccination With Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and *Haemophilus Influenzae* Type b

Yuelian Sun, PhD
Jakob Christensen, PhD
Anders Hviid, PhD
Jiong Li, PhD
Peter Vedsted, PhD
Jørn Olsen, PhD
Mogens Vestergaard, PhD

Context Vaccination with whole-cell pertussis vaccine carries an increased risk of febrile seizures, but whether this risk applies to the acellular pertussis vaccine is not known. In Denmark, acellular pertussis vaccine has been included in the combined diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccine since September 2002.

Objective To estimate the risk of febrile seizures and epilepsy after DTaP-IPV-Hib vaccination given at 3, 5, and 12 months.

Design, Setting, and Participants A population-based cohort study of 378 834 children who were born in Denmark between January 1, 2003, and December 31, 2008, and followed up through December 31, 2009; and a self-controlled case series (SCCS) study based on children with febrile seizures during follow-up of the cohort.

Main Outcome Measures Hazard ratio (HR) of febrile seizures within 0 to 7 days (0, 1-3, and 4-7 days) after each vaccination and HR of epilepsy after first vaccination in the cohort study. Relative incidence of febrile seizures within 0 to 7 days (0, 1-3, and 4-7 days) after each vaccination in the SCCS study.

Results A total of 7811 children were diagnosed with febrile seizures before 18 months, of whom 17 were diagnosed within 0 to 7 days after the first (incidence rate, 0.8 per 100 000 person-days), 32 children after the second (1.3 per 100 000 person-days), and 201 children after the third (8.5 per 100 000 person-days) vaccinations. Overall, children did not have higher risks of febrile seizures during the 0 to 7 days after the 3 vaccinations vs a reference cohort of children who were not within 0 to 7 days of vaccination. However, a higher risk of febrile seizures was found on the day of the first (HR, 6.02; 95% CI, 2.86-12.65) and on the day of the second (HR, 3.94; 95% CI, 2.18-7.10), but not on the day of the third vaccination (HR, 1.07; 95% CI, 0.73-1.57) vs the reference cohort. On the day of vaccination, 9 children were diagnosed with febrile seizures after the first (5.5 per 100 000 person-days), 12 children after the second (5.7 per 100 000 person-days), and 27 children after the third (13.1 per 100 000 person-days) vaccinations. The relative incidences from the SCCS study design were similar to the cohort study design. Within 7 years of follow-up, 131 unvaccinated children and 2117 vaccinated children were diagnosed with epilepsy, 813 diagnosed between 3 and 15 months (2.4 per 1000 person-years) and 1304 diagnosed later in life (1.3 per 1000 person-years). After vaccination, children had a lower risk of epilepsy between 3 and 15 months (HR, 0.63; 95% CI, 0.50-0.79) and a similar risk for epilepsy later in life (HR, 1.01; 95% CI, 0.66-1.56) vs unvaccinated children.

Conclusions DTaP-IPV-Hib vaccination was associated with an increased risk of febrile seizures on the day of the first 2 vaccinations given at 3 and 5 months, although the absolute risk was small. Vaccination with DTaP-IPV-Hib was not associated with an increased risk of epilepsy.

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STUDIES HAVE REPORTED INcreased risks of febrile seizures shortly after administration of whole-cell pertussis vaccine,[1,2] as would be expected since the whole-cell pertussis vaccine often causes fever. Whole-cell pertussis vaccine has also been associated with serious neurological illnesses characterized by seizures and intellectual impairment,[3,4] but recent studies indicate that the vaccination only triggers an earlier onset of severe epileptic encephalopathy in children with sodium channel gene mutations.[5-7] The acellular pertussis vaccine has replaced the whole-cell pertussis vaccine in most countries because the efficacy of the acellular vaccine is comparable with the whole-cell vaccine and it has substantially fewer adverse effects, including fever.[8-12] Previous randomized controlled trials did not reveal differences in the risk of seizures after acellular pertussis vaccination compared with whole-cell pertussis vaccination, but the trials were not powered to detect rare adverse effects.[8-11] A study from the United Kingdom found a 2-fold higher risk of seizures on the day of the diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccination, and a study from the United States found a 30% higher risk of seizures on the day of the first DTaP vac-

Author Affiliations are listed at the end of this article.
Corresponding Author: Yuelian Sun, PhD, Department of Public Health, Aarhus University, Bartholins Allé 2, DK-8000 Aarhus C, Denmark (ys@soci.au.dk).

cination.[13,14] However, these estimates did not reach statistical significance and the studies did not distinguish between afebrile and febrile seizures.[13,14] We examined the risk of febrile seizures and epilepsy after DTaP-IPV-Hib vaccination in a large nationwide, population-based cohort study in Denmark.

METHODS

Study Population

We established a cohort of 388 817 children who were born in Denmark between January 1, 2003, and December 31, 2008. We excluded 9983 children who died, emigrated, received a diagnosis of febrile seizures or epilepsy during their first 3 months of life, or had a missing value on sex, birth weight, gestational age, and parity of the mother, which resulted in 378 834 children (97.4%) in the analysis. The cohort was identified by using information from the Danish Civil Registry,[15] which stores information on all persons living in Denmark. The unique personal identification number was used for accurate linkage of all registers at the individual level. The study was approved by the Danish Data Protection Agency. We conducted 2 analyses on the same data set (a cohort analysis and a self-controlled case series [SCCS] study analysis).[16,17] The SCCS method is used to investigate the association between a transient exposure and an adverse event. The SCCS analysis includes cases that act as their own controls; the observation time of cases is classified as risk and control periods. The relative incidence is estimated as the incidence of the event during the risk periods relative to the incidence during the control periods. In this design,[16,17] confounding factors that do not vary during the study period, such as genes, socioeconomic status, sex, or underlying diseases, are controlled.

Vaccination

Information on vaccinations was obtained from reports submitted from general practitioners (GPs) to the Danish Health Insurance Registry. Approximately 98% of the Danish population is listed with a GP who provides all routine childhood vaccinations. The vaccinations are free of charge and GPs are reimbursed by the Public Health System based on their reports to the Danish Health Insurance Registry. Unlike our previous studies, we had access to data on the day of vaccination instead of only the week of vaccination.[18,19]

The acellular pertussis vaccine was introduced in Denmark on January 1, 1997, as part of the combined DTaP-IPV vaccine; Hib was added to the vaccine on September 1, 2002.[12] The recommended vaccination schedule is 3, 5, and 12 months, with a booster at 5 years. A pneumococcal vaccine was included in the Danish childhood vaccination program on October 1, 2007, and follows the same schedule. Three codes (8341, 8342, 8343) were used in the register for vaccinations given at 3, 5, and 12 months.

Only 1 record was included for repeated reports for the same vaccination (n=3635). We included the record closest to the vaccine schedule if different dates were reported for the same vaccination code (n=18 678). We included the first vaccination if different vaccination codes were reported on the same day (n=742). We also excluded children with vaccination records in a reverse order (n=3976) (eg, if the date of the second vaccination was registered before the date of the first vaccination).

After data cleaning, 32 370 children (8.4%) had a missing value on the first vaccination, 20 263 (5.3%) on the second vaccination, and 6121 (1.6%) on both the first and the second vaccination. We included these children in the analyses by using the available data.

Outcomes

Information on febrile seizures and epilepsy was obtained from the Danish National Hospital Register,[20] in which diseases were recorded according to the Danish version of the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*). We identified children with febrile seizures if they were registered with the *ICD-10* code R56.0, were older than 3 months, and had no history of epilepsy. Children with epilepsy were identified by *ICD-10* codes G40-41. Both inpatients and outpatients were included.

Confounders

Data on birthday, sex, gestational age, birth weight, and parity of the mother were obtained from the Danish Birth Registry.[21] Information on parental history of epilepsy (*International Classification of Diseases, Eighth Revision* [*ICD-8*]: 345 and *ICD-10*: G40-G41) was obtained from the Danish National Hospital Register.[20] Information on maternal education and family income at the time of birth was obtained from Statistics Denmark. Information on education and income was not available for children born in 2008; therefore, we used information from 2007 or 2006 (if data from 2007 were missing). Children with missing values on education were grouped separately (n=8679). Maternal education was categorized according to years of education (≤9 years, 10-12 years, ≥13 years, and missing). Family income at the time of birth was based on the sum of the parents' income and was categorized into quartiles according to calendar year of birth. Children with missing information on their parents' income were grouped separately (n=11 778).

Statistical Methods

Risk of Febrile Seizures. We estimated the association between vaccination and the risk of febrile seizures in the cohort study using Cox proportional hazard regression models. Children were followed up from age 90 days until the onset of febrile seizures, epilepsy, death, emigration, age 18 months, or the end of the study (December 31, 2009), whichever occurred first. Children who were diagnosed with epilepsy and febrile seizures on the same day were categorized with epilepsy.

Vaccination was treated as a time-dependent variable. Children entered the reference cohort at the beginning of follow-up and moved to the exposed cohort on the day of vaccina-

tion. The children remained in the exposed cohort for 8 days (0-7 days) and then returned to the reference cohort until the day of the next vaccination. Thus, both unvaccinated children and vaccinated children contributed person-years at risk to the reference cohort. The day of vaccination was defined as day 0. We calculated the follow-up time from 8 AM until midnight on the day of vaccination because no children were vaccinated before 8 AM. We allocated the preceding 8 hours into the reference cohort.

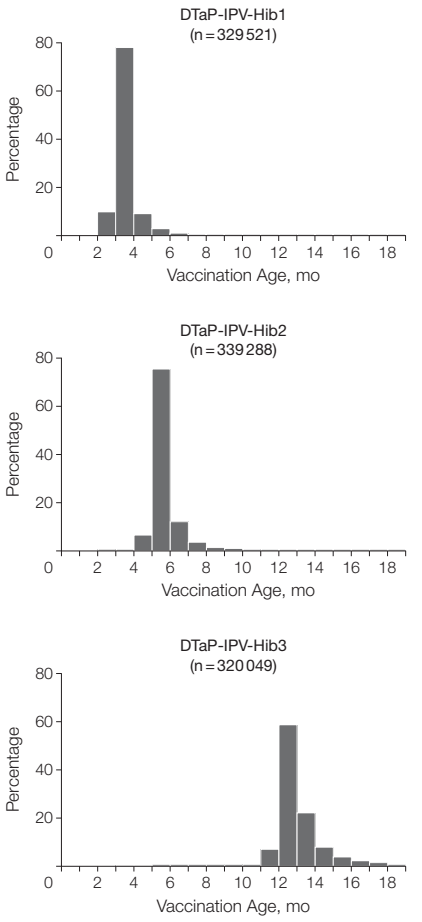
We estimated hazard ratios (HRs) of febrile seizures within 0 to 7 days of vaccination compared with a reference group of children who were not within 0 to 7 days of vaccination. We further estimated HRs of febrile seizures within 0, 1 to 3, and 4 to 7 days of vaccination compared with the reference children. Age was used as the time scale in the Cox proportional hazard regression model.[22] In the multivariate model, we adjusted for the child's sex, multiple births, calendar year of birth, season, gestational age, birth weight, parity of the mother, parental history of epilepsy, maternal education, and family income at the time of birth. Season was included as a time-varying variable.

We estimated the HRs of febrile seizures separately for boys and girls. We also examined HRs of febrile seizures for children who received their vaccination according to the time schedule suggested by the vaccination program (first dose at 3 months [90-119 days], second dose at 5 months [150-179 days], and third dose at 12 months [360-389 days]), and children vaccinated after the introduction of the pneumococcal vaccine (ie, born after July 1, 2007).

The SCCS analyses included the 7811 children diagnosed with febrile seizures during the study period and estimated the association between DTaP-IPV-Hib vaccination and risk of the first episode of febrile seizures. For each child, the observation period began when the child was 90 days old and lasted until the child was 540 days old (18 months), the day of emigration, the day of death, or December 31, 2009, whichever came first. The observation period was divided into a risk period (0-7 days after vaccination) and a control period (the remaining part of the observation period). We estimated the relative incidence of febrile seizures in the risk periods of 0 days, 1 to 3 days, 4 to 7 days, and 0 to 7 days after vaccination compared with the incidence of febrile seizures for the control period, using a conditional Poisson regression model with adjustment for the age of the child (1-week interval) and the season of the observation period. We also estimated the relative incidences of febrile seizures during a 15-day period before and a 15-day period after vaccination compared with the control period (the rest of the observation time) to show the trend of the risk of febrile seizures. In addition, we excluded a 2-week prevaccination period from the control period and reestimated the relative incidence of febrile seizures within 0 days, 1 to 3 days, 4 to 7 days, and 0 to 7 days after vaccination to eliminate the potential bias introduced by delayed vaccination due to febrile seizures or general ill health.

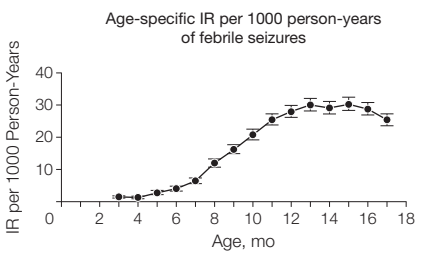
Prognosis of Febrile Seizures Following DTaP-IPV-Hib Vaccination. We compared the risk of recurrent febrile seizures and the risk of epilepsy in children whose first febrile seizures occurred within 0 to 7 days after vaccination (n=250) with those whose first febrile seizures did not occur within 0 to 7 days after vaccination (n=7561). We examined the risk after the first, second, and third vaccinations separately. Using a Cox proportional hazard regression model, we followed up these children from the day of their first diagnosis of febrile seizures until a second episode of febrile seizures or a first diagnosis of epilepsy, death, emigration, or December 31, 2009, whichever came first. We treated all febrile seizures occurring within 3 days as 1 episode. We adjusted for the same factors as in the analyses of the incidence of febrile seizures and for the onset age of the first febrile seizures (1-week interval).

Figure 1. Age at Time of DTaP-IPV-Hib Vaccination



DTaP-IPV-Hib indicates diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b. For DTaP-IPV-Hib1, median (interquartile range [IQR]) vaccination age was 3 (2-4) months, with percentage ranges of 0.01% to 0.22% between 7 and 17 months; for DTaP-IPV-Hib2, median (IQR) vaccination age was 5 (4-7) months, with 0.05% at 3 months and 0.04% to 0.36% between 10 and 17 months; and for DTaP-IPV-Hib3, median (IQR) vaccination age was 12 (11-15) months, with 0.01% to 0.12% between 4 and 10 months.

Figure 2. Age-Specific IR of Febrile Seizures per 1000 Person-Years (N=378 834)



IR indicates incidence rate. Error bars represent 95% CIs.

Risk of Epilepsy. The study population for epilepsy (N = 378 883) was similar to the study population for febrile seizures except that we included children diagnosed with febrile seizures in the first 3 months of life. We estimated the risk of epilepsy in children after the first DTaP-IPV-Hib vaccination using the Cox proportional hazard regression model. Children were followed up for up to 7 years from aged 90 days until the onset of epilepsy, death, emigration, or December 31, 2009, whichever occurred first. Vaccination was treated as a time-varying exposure variable. Children entered the unvaccinated cohort at the beginning of the follow-up. On the day of the first vaccination, they entered and remained in the exposed cohort. We adjusted for the same factors as in the analyses of incidence of febrile seizures. We tested the proportional assumption for the risk of epilepsy during follow-up and found that the HRs of epilepsy in the early period of life and later in life differed. We therefore reported the HRs of epilepsy for vaccinated children in the first 15 months of life and later in life separately.

All the analyses were performed in STATA version 11.1 (StataCorp LP) using a 2-sided significance level of .05.

Table 1. Characteristics of 7811 Children With Febrile Seizures According to Vaccination Status

Characteristics	No. (%) of Children Diagnosed With Febrile Seizures		
	In the Reference Cohort (n = 7561)	Within 0-7 Days After Vaccination (n = 250)	On the Day of Vaccination (n = 48)
Sex			
Boys	4129 (54.6)	134 (53.6)	27 (56.3)
Girls	3432 (45.4)	116 (46.4)	21 (43.8)
Multiple birth			
Singletons	7279 (96.3)	243 (97.2)	46 (95.8)
Twins or higher (multiple births)	282 (3.7)	7 (2.8)	2 (4.2)
Gestational age			
Term (37-41 wk)	6535 (86.4)	216 (86.4)	43 (89.6)
Preterm (<37 wk)	604 (8.0)	15 (6.0)	3 (6.3)
Postterm (≥42 wk)	422 (5.6)	19 (7.6)	2 (4.2)
Birth weight, g			
<2500	446 (5.9)	10 (4.0)	1 (2.1)
2500-2999	938 (12.4)	32 (12.8)	5 (10.4)
3000-3499	2404 (31.8)	80 (32.0)	10 (20.8)
3500-3999	2436 (32.2)	81 (32.4)	21 (43.8)
≥4000	1337 (17.7)	47 (18.8)	11 (22.9)
Parity of the mother			
1	3568 (47.2)	127 (50.8)	30 (62.5)
≥2	3993 (52.8)	123 (49.2)	18 (37.5)
Season of diagnosis			
Winter (December-February)	1792 (23.7)	51 (20.4)	13 (27.1)
Spring (March-May)	2310 (30.6)	83 (33.2)	14 (29.2)
Summer (June-August)	1920 (25.4)	63 (25.2)	12 (25.0)
Autumn (September-November)	1539 (20.4)	53 (21.2)	9 (18.8)
Parental history of epilepsy			
No	7185 (95.0)	237 (94.8)	43 (89.6)
Yes	376 (5.0)	13 (5.2)	5 (10.4)
Maternal education, y			
≤9	1382 (18.3)	47 (18.8)	17 (35.4)
10-12	3079 (40.7)	99 (39.6)	16 (33.3)
≥13	2976 (39.4)	99 (39.6)	14 (29.2)
Missing	124 (1.6)	5 (2.0)	1 (2.1)
Quartile of family income (median DKK, US$)[a]			
1 (323 677 kr, $57 135)	1850 (24.5)	61 (24.4)	15 (31.3)
2 (482 055 kr, $85 091)	1890 (25.0)	66 (26.4)	10 (20.8)
3 (590 305 kr, $104 199)	1798 (23.8)	58 (23.2)	10 (20.8)
4 (783 552 kr, $138 311)	1674 (22.1)	53 (21.2)	11 (22.9)
Missing[b]	349 (4.6)	12 (4.8)	2 (4.2)
Type of patient			
Outpatient	3450 (45.6)	122 (48.8)	17 (35.4)
Inpatient	4111 (54.4)	128 (51.2)	31 (64.6)

[a] DKK indicates Danish currency (ie, Danish krone); US conversion as of February 1, 2012.
[b] Missing quartile indicates family income at the time of birth in a group of children with a missing value on the income of 1 of the parents.

RESULTS

Among the 378 834 children, 329 521 (87.0%) were exposed to the first DTaP-IPV-Hib vaccination, 339 288 (90.0%) to the second, and 320 049 (84.5%) to the third during the follow-up from 3 to 18 months, while 6854 (1.8%) children did not receive any DTaP-IPV-Hib vaccines. Overall, 7811 (2.1%) were diagnosed with febrile seizures before 18 months. FIGURE 1 shows the age distribution at each vaccination and FIGURE 2 shows the age-specific incidence rate of febrile seizures in the study population. TABLE 1 shows the characteristics of the 7811 children with febrile seizures according to vaccination status.

Of the 7811 children with febrile seizures, 17 were diagnosed within 0 to 7 days after the first vaccination (incidence rate, 0.8 per 100 000 person-days), 32 within 0 to 7 days after the second vaccination (incidence rate, 1.3 per 100 000 person-days), and 201 within 0 to 7 days after the third vaccination (incidence rate, 8.5 per 100 000 person-days). Children did not have higher risks of febrile seizures during the 0 to 7 days after the 3 vaccinations compared with a reference cohort of children who were not within 0 to 7 days of vaccination (TABLE 2). However, a higher risk of febrile seizures was found on the day of the first vaccina-

tion (HR, 6.02; 95% CI, 2.86-12.65) and on the day of the second vaccination (HR, 3.94; 95% CI, 2.18-7.10), but not on the day of the third vaccination (HR, 1.07; 95% CI, 0.73-1.57) compared with the reference cohort (Table 2). On the day of vaccination, 9 children were diagnosed with febrile seizures after the first vaccination (incidence rate, 5.5 per 100 000 person-days), 12 after the second vaccination (incidence rate, 5.7 per 100 000 person-days), and 27 after the third vaccination (incidence rate, 13.1 per 100 000 person-days). The relative incidences from the SCCS study design were similar to the HRs from the cohort study (Table 2).

The results did not change when we restricted the analyses to girls, boys, children who received the vaccination according to the time schedule suggested by the vaccination program, or children who were vaccinated after the introduction of the pneumococcal vaccine (TABLE 3 and TABLE 4). Children who received pneumococcal vaccine together with DTaP-IPV-Hib vaccine also had an increased risk of febrile seizures within 1 to 3 days after the second vaccination and on the day of the third vaccination (Table 4).

The SCCS study showed that the incidence of febrile seizures was lower during a 2-week period before vaccination compared with the reference period (FIGURE 3). The relative incidences of febrile seizures within 0 to 7 days after vaccination were slightly reduced when the 2-week low-risk pre-

Table 2. Relative Risk of Febrile Seizures After DTaP-IPV-Hib Vaccination According to Types of Analysis

Analysis Method	Time After DTaP-IPV-Hib Vaccination, d			
	0	1-3	4-7	0-7
First Vaccination				
Cohort analysis[a]				
No. of vaccinations[b]	298 311	317 741	329 138	329 521
Person-time, d[c]	199 864	937 253	1 300 813	2 437 930
Children with febrile seizures	9	6	2	17
Crude HR	6.05	1.40	0.41	1.64
Adjusted HR (95% CI)[d]	6.02 (2.86-12.65)	1.38 (0.58-3.31)	0.41 (0.10-1.69)	1.64 (0.93-2.88)
SCCS analysis[e]				
Relative IR (95% CI)[f]	6.49 (3.10-13.61)	1.47 (0.62-3.50)	0.44 (0.11-1.81)	1.65 (0.94-2.90)
Sensitivity relative IR (95% CI)[g]	4.95 (2.24-10.92)	1.16 (0.47-2.86)	0.38 (0.09-1.59)	1.37 (0.75-2.49)
Second Vaccination				
Cohort analysis[a]				
No. of vaccinations[b]	339 276	339 252	339 196	339 288
Person-time, d[c]	227 312	1 017 679	1 356 647	2 601 638
Children with febrile seizures	12	14	6	32
Crude HR	3.94	1.57	0.52	1.36
Adjusted HR (95% CI)[d]	3.94 (2.18-7.10)	1.57 (0.91-2.72)	0.52 (0.23-1.18)	1.36 (0.93-1.98)
SCCS analysis[e]				
Relative IR (95% CI)[f]	3.97 (2.20-7.16)	1.52 (0.88-2.64)	0.49 (0.22-1.11)	1.32 (0.90-1.92)
Sensitivity relative IR (95% CI)[g]	3.28 (1.79-6.01)	1.31 (0.74-2.30)	0.46 (0.20-1.04)	1.17 (0.79-1.73)
Third Vaccination				
Cohort analysis[a]				
No. of vaccinations[b]	320 049	319 846	319 473	320 049
Person-time, d[c]	214 395	959 178	1 277 071	2 450 644
Children with febrile seizures	27	68	106	201
Crude HR	1.07	0.89	1.06	1.00
Adjusted HR (95% CI)[d]	1.07 (0.73-1.57)	0.89 (0.70-1.14)	1.06 (0.87-1.28)	0.99 (0.86-1.15)
SCCS analysis[e]				
Relative IR (95% CI)[f]	1.07 (0.73-1.57)	0.89 (0.70-1.14)	1.05 (0.86-1.28)	0.99 (0.86-1.15)
Sensitivity relative IR (95% CI)[g]	0.98 (0.67-1.43)	0.81 (0.64-1.04)	0.96 (0.79-1.17)	0.91 (0.78-1.05)

Abbreviations: DTaP-IPV-Hib, diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b vaccine; HR, hazard ratio; IR, incidence rate; SCCS, self-controlled case series study.

[a] The reference cohort included nonvaccinated children and children who were not in the risk period (0-7 days) of vaccination.

[b] Number of vaccinations in groups 0 days, 1 to 3 days, or 4 to 7 days is less than the total vaccination in group 0 to 7 days, especially for the first 2 vaccinations because children vaccinated between 82 to 89 days were counted as the exposed differently in groups 0 days, 1 to 3 days, 4 to 7 days, or 0 to 7 days, depending on the vaccination age.

[c] The person-days on the day of vaccination is less than the number of vaccinations because we calculated the follow-up time from 8 AM until midnight on the day of vaccination since no children were vaccinated before 8 AM (ie, follow-up time was only two-thirds of a day).

[d] Adjusted for the child's sex, multiple birth, calendar year of birth (1-year interval), seasons of birth, gestational age, birth weight, parity of the mother, parental history of epilepsy, maternal education, and family income at the time of birth. See Table 1 for characteristics of variables.

[e] The SCCS study included 7811 children with febrile seizures.

[f] Adjusted for the child's age in 1-week intervals and season as a time-varying variable.

[g] The sensitivity analysis included a 2-week prevaccination period to allow for a possible delay of vaccination following an episode of febrile seizures. The relative IR of febrile seizures in a 2-week period was 0.46 (95% CI, 0.20-1.09) before the first, 0.48 (95% CI, 0.30-0.77) before the second, and 0.49 (95% CI, 0.43-0.57) before the third vaccinations. The control period was the observation time outside the 2-week period before vaccination and the 0- to 7-day risk period after vaccination.

vaccination period was excluded from the control period (Table 2).

Among the 250 children whose first febrile seizures occurred within 0 to 7 days of vaccination, 80 (32.0%) had a recurrent episode of febrile seizures and 8 (3.2%) developed epilepsy later in life. Among the 7561 children whose first febrile seizures did not occur within 0 to 7 days after DTaP-IPV-Hib vaccination, 2207 (29.2%) had recurrent febrile seizures and 208 (2.8%) developed epilepsy later in life. Children whose first febrile seizures occurred within 0 to 7 days of the vaccination had almost the same risk of recurrent febrile seizures (HR, 1.09; 95% CI, 0.86-1.38) and epilepsy (HR, 0.61; 95% CI, 0.27-1.40) as those whose first febrile seizures did not occur within 0 to 7 days of vaccination (eTable, available at http://www.jama.com). The results did not change when the risk of recurrent febrile seizures and epilepsy were examined for children whose first febrile seizures occurred within 0 to 7 days after the first, second, or third vaccination (eTable).

Within 7 years of follow-up, 2248 children were diagnosed with epilepsy, 131 unvaccinated children (45 125 person-years of follow-up) and 2117 vaccinated children (1 514 769 person-years of follow-up). Among 2117 children diagnosed with epilepsy after vaccination, 813 were diagnosed between 3 and 15 months (incidence rate, 2.4 per 1000 person-years) and 1304 were diagnosed later in life (incidence rate, 1.3 per 1000 person-years), but only 2 children were diagnosed with epilepsy on the day of the first vaccination and 1 on the day of the second vaccination. Compared with the unvaccinated cohort, vaccinated children had a lower risk of epilepsy in the first 15 months of life (HR, 0.63; 95% CI, 0.50-0.79) but had a similar risk of epilepsy afterward (HR, 1.01; 95% CI, 0.66-1.56).

Table 3. Hazard Ratios (HRs) of Febrile Seizures After DTaP-IPV-Hib Vaccination in Boys and Girls of the Cohort Study[a]

	Timing After DTaP-IPV-Hib Vaccination, d			
	0	1-3	4-7	0-7
Boys				
First vaccination				
Person-time, d	102 347	480 137	666 485	1 248 969
Children with febrile seizure	6	5	1	12
Adjusted HR (95% CI)	5.97 (2.39-14.92)	1.71 (0.64-4.54)	0.32 (0.04-2.35)	1.78 (0.90-3.52)
Second vaccination				
Person-time, d	116 452	521 354	694 991	1 332 797
Children with febrile seizure	6	7	4	17
Adjusted HR (95% CI)	3.59 (1.56-8.25)	1.41 (0.65-3.05)	0.61 (0.22-1.65)	1.31 (0.78-2.19)
Third vaccination				
Person-time, d	109 445	489 636	651 931	1 251 012
Children with febrile seizure	15	35	55	105
Adjusted HR (95% CI)	1.10 (0.66-1.83)	0.83 (0.60-1.17)	1.01 (0.77-1.32)	0.95 (0.78-1.16)
Girls				
First vaccination				
Person-time, d	97 517	457 116	634 328	1 188 961
Children with febrile seizure	3	1	1	5
Adjusted HR (95% CI)	6.13 (1.72-21.79)	0.72 (0.09-5.57)	0.56 (0.07-4.35)	1.37 (0.49-3.77)
Second vaccination				
Person-time, d	110 860	496 325	661 656	1 268 841
Children with febrile seizure	6	7	2	15
Adjusted HR (95% CI)	4.36 (1.89-10.07)	1.78 (0.82-3.86)	0.41 (0.10-1.66)	1.43 (0.83-2.46)
Third vaccination				
Person-time, d	104 950	469 542	625 140	1 199 632
Children with febrile seizure	12	33	51	96
Adjusted HR (95% CI)	1.04 (0.59-1.84)	0.96 (0.68-1.36)	1.12 (0.84-1.48)	1.05 (0.85-1.30)

Abbreviation: DTaP-IPV-Hib, diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b vaccine.

[a]The reference cohort included nonvaccinated children and children who were not in the risk period (0-7 days) of vaccination. Adjusted HR was adjusted for multiple birth, calendar year of birth (1-year interval), seasons of birth, gestational age, birth weight, parity of the mother, parental history of epilepsy, maternal education, and family income at the time of birth.

COMMENT

In this large, population-based cohort study, we found that the relative risks of febrile seizures were increased on the day of the first and the second vaccinations, but the absolute risks were low (<4 per 100 000 vaccinations) and the overall risk of febrile seizures was not increased within 0 to 7 days after DTaP-IPV-Hib vaccinations. The risks of recurrent febrile seizures or subsequent epilepsy were not increased for children whose first febrile seizure occurred within 0 to 7 days of vaccination. The risk of epilepsy was not higher among vaccinated vs unvaccinated children.

An SCCS study from the United Kingdom examined the risk of seizures after DTaP-IPV-Hib vaccination was given at 2, 3, and 4 months and found a 2-fold higher risk of seizures on the day of vaccination.[14] A combined cohort and SCCS study from the United States examined the risk of seizures after DTaP vaccination given at 2, 4, 6, and 15 to 18 months and found a 30% higher risk of seizures on the day of the first DTaP vaccination.[13] The estimates of these studies were weaker than our study, probably because they

did not distinguish between afebrile and febrile seizures.[13,14] The acellular pertussis vaccines in the studies from the United Kingdom and probably from the United States have multiple components of pertussis antigen,[13,14] whereas the pertussis vaccine in Denmark contains only 1 pertussis antigen, the pertussis toxoid.

Our study had almost complete follow-up of all children born in Denmark during a 6-year period due to nationwide registries. Both inpatients and outpatients were included in the register system and selection bias cannot explain our findings. Information on vaccination and febrile seizures was collected prospectively by health care professionals and did not rely on parental recall. We expect the data quality of the DTaP-IPV-Hib vaccination to be high because all GPs in Denmark use computers to document their services as a matter of routine and are reimbursed only after reporting immunization data to the National Board of Health. Children with missing values on vaccination remained in the reference cohort and tended to bias the association toward the null hypothesis. During the study period, the schedule and dosing of DTP-IPV-Hib vaccine did not change. We, and other studies, have previously shown that the risk of febrile seizures is higher in the second week after the measles, mumps, and rubella (MMR) vaccination.[1,19,23] Thus, the MMR vaccination can theoretically confound the association between DTaP-IPV-Hib vaccination and febrile seizures if children were vaccinated with MMR 1 to 2 weeks before DTaP-IPV-Hib vaccination. In Denmark, the first MMR vaccination is scheduled at 15 months, 3 months after the last DTaP-IPV-Hib vaccination.

In the early 1990s, the quality of febrile seizures registration in the Danish National Hospital Register was estimated by following a cohort of 6624 children for 10 years.[24] The positive predictive value of a febrile seizure diagnosis was 93% (95% CI, 89%-96%) and the completeness was 72% (95% CI, 66%-76%).[24] We expect, however, that the completeness of febrile seizures was even higher in this study, because outpatients have been included in the National Hospital Register since 1995. The incidence of febrile seizures in our study was higher than what has been reported in other studies.[13] The positive predictive value of epilepsy diagnoses in the registry has been estimated to be 81% (95% CI, 75%-87%).[25] Unfortunately, we do not have information on completeness for epilepsy. Any misclassification of febrile seizures or epilepsy is likely to be nondifferential and cause a bias of the HR toward the null hypothesis, but we expect this bias to be small. An incomplete registration of febrile seizures or epilepsy could underestimate the incidence of the 2 disorders, but it has probably not af-

Table 4. Hazard Ratios (HRs) of Febrile Seizures After DTaP-IPV-Hib Vaccination in Children Vaccinated According to the Schedule and After the Pneumococcal Vaccine Was Introduced in the Vaccine Program in the Cohort Study[a]

	Timing After DTaP-IPV-Hib Vaccination, d			
	0	1-3	4-7	0-7
Children Vaccinated According to the Schedule of the Vaccination Program[b]				
First vaccination				
Person-time, d	172 277	771 349	1 028 385	1 972 011
Children with febrile seizure	9	5	1	15
Adjusted HR (95% CI)	7.69 (3.49-16.92)	1.47 (0.55-3.92)	0.31 (0.04-2.31)	2.19 (1.14-4.21)
Second vaccination				
Person-time, d	171 416	767 463	1 023 181	1 962 060
Children with febrile seizure	8	8	2	18
Adjusted HR (95% CI)	4.39 (2.08-9.26)	1.53 (0.73-3.21)	0.32 (0.08-1.30)	1.37 (0.81-2.32)
Third vaccination				
Person-time, d	125 153	560 248	746 682	1 432 083
Children with febrile seizure	15	42	68	125
Adjusted HR (95% CI)	1.03 (0.62-1.72)	0.95 (0.69-1.29)	1.17 (0.91-1.50)	1.07 (0.89-1.29)
Children Vaccinated After the Pneumococcal Vaccine Was Introduced in the Vaccine Program[c]				
First vaccination				
Person-time, d	51 146	239 654	333 668	624 468
Children with febrile seizure	4	2	0	6
Adjusted HR (95% CI)	6.64 (2.07-21.33)	1.20 (0.26-5.42)	NA	1.55 (0.59-4.07)
Second vaccination				
Person-time, d	58 349	261 221	348 239	667 809
Children with febrile seizure	5	8	2	15
Adjusted HR (95% CI)	4.28 (1.69-10.84)	2.42 (1.14-5.14)	0.52 (0.13-2.15)	1.80 (1.02-3.20)
Third vaccination				
Person-time, d	52 681	235 703	313 860	602 244
Children with febrile seizure	14	14	28	56
Adjusted HR (95% CI)	2.45 (1.44-4.17)	0.81 (0.48-1.38)	1.23 (0.84-1.80)	1.23 (0.93-1.62)

Abbreviations: DTaP-IPV-Hib, diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b vaccine; NA, not available.

[a] The reference cohort included nonvaccinated children and children who were not in the risk period (0-7 days) of vaccination. Adjusted HR was adjusted for the child's sex, multiple birth, calendar year of birth (1-year interval), seasons of birth, gestational age, birth weight, parity of the mother, parental history of epilepsy, maternal education, and family income at the time of birth.

[b] Children who received their first DTaP-IPV-Hib vaccination at 3 months (90-119 days), the second at 5 months (150-179 days), and the third at 12 months (360-389 days).

[c] Children born after July 1, 2007, and received the pneumococcal vaccine together with the DTaP-IPV-Hib vaccine due to a change in the Danish childhood vaccination program on October 1, 2007.

fected the relative risks because hospital registration is unlikely to depend on vaccination status.

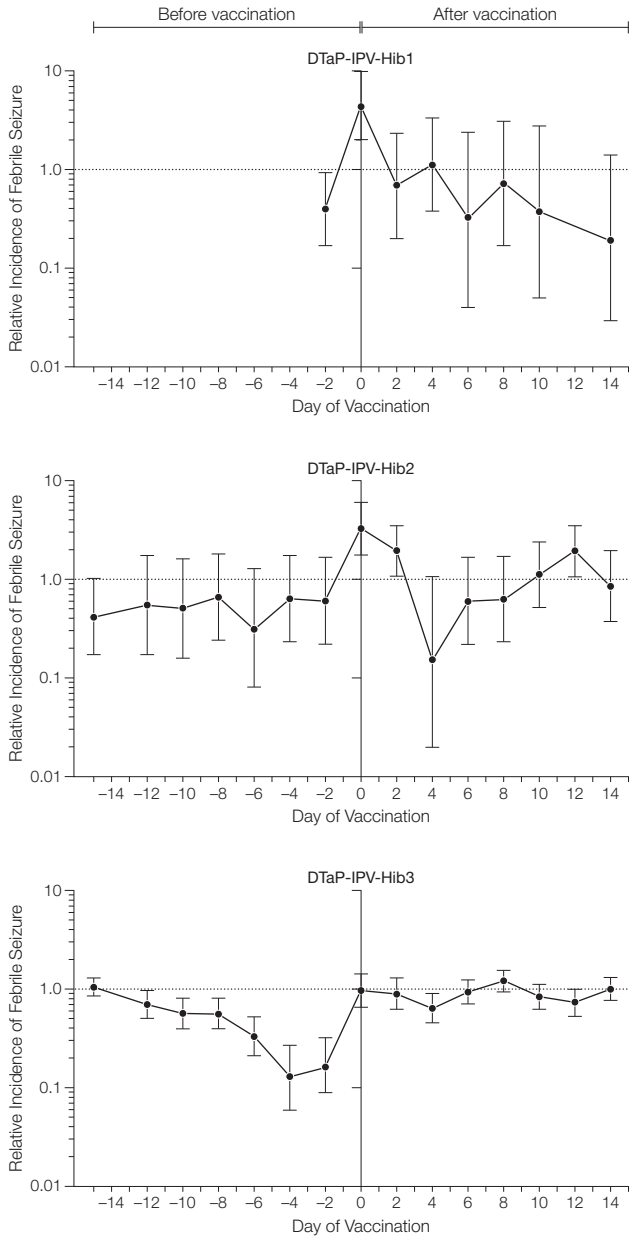
Vaccinations may correlate with social factors, such as income, parental education, and family size,[26] but our estimates did not change when we adjusted for several potential confounding factors, including socioeconomic factors. The SCCS study controlled for all time-stable confounders and showed similar findings. The estimates of the risk for febrile seizures could be affected by delayed vaccination due to either febrile seizures or general ill health. We conducted a sensitivity analysis excluding the 2 weeks before vaccination.[17] These results were in line with the main analyses, supporting that delayed vaccination has not significantly biased our results.

Because febrile seizures are rare events during the first 6 months, it requires a large study population to detect a moderately increased risk of febrile seizures after vaccination. The power to detect an increased relative risk of 2 for febrile seizures within 0 to 7 days of the first vaccination was 59% given the size of the study population (n = 378 834), the probability of febrile seizure at 3 months (1.38 per 1000 person-years), a .05 significance level, and the proportion of children receiving vaccination at 3 months (68%). The power increased to 98% to detect an increased relative risk of 3.

It is unclear why the HRs of febrile seizure increased only after the first 2 vaccinations but not after the third vaccination when the underlying incidence of febrile seizures was higher. There may be more competing risk factors for febrile seizures during a period in which the incidence of febrile seizures is high and the relative importance of a single risk factor like vaccination may be lower.

Fever is a common adverse effect of vaccinations and a necessary cause of febrile seizures. The transient increased risks of febrile seizures on the day of vaccination were followed up by a slightly lower risk in the days following. This suggests that the vaccination may have induced febrile seizures that would have occurred a few days later anyway, or that recently vaccinated children constitute a select group of relatively healthy children. It is unclear why vaccinated children showed a decreased risk of epilepsy between 3 and 15 months but it may be due to unmeasured confounding. Unfortunately, we had no data to evaluate

Figure 3. Relative Incidence of Febrile Seizures During 15 Days Before and 15 Days After DTaP-IPV-Hib Vaccination From the SCCS Study



DTaP-IPV-Hib indicates diphtheria-tetanus toxoids-acellular pertussis–inactivated poliovirus–*Haemophilus influenzae* type b; SCCS, self-controlled case series study. Error bars indicate 95% CIs. The SCCS study comprised 7811 children with febrile seizures. The reference is the incidence of febrile seizures in the control observation time that is outside the two 15-day periods. The average relative incidence of febrile seizures in the 15-day period before DTaP-IPV-Hib1 vaccination is presented only due to the limited number of children in each shorter period of the 15-day observation time. Horizontal dotted lines indicate a relative incidence of 1.0.

whether children with a high risk of epilepsy, such as those with severe neurological disorders, were less likely to be vaccinated.

Public awareness of possible adverse effects following whole-cell pertussis vaccination has caused a reduction in immunization rates and outbreaks of whooping cough in several countries.[27] The DTaP-IPV-Hib vaccine was given as a combined vaccine throughout the study period; therefore, we were unable to disentangle which of the components caused febrile seizures on the day of vaccination. Previous studies have shown that the DTaP vaccine has a pattern of adverse events similar to that of diphtheria and tetanus vaccine.[8-10] The estimates did not change when pneumococcal vaccine was added to the vaccination program, although we also found an increased risk of febrile seizures 1 to 3 days after the second vaccination and on the day of the third vaccination, which could be a chance finding.[28]

Although the relative risks of febrile seizures on the day of the 2 DTaP-IPV-Hib vaccinations were increased, the absolute risk of febrile seizures after DTaP-IPV-Hib vaccination was very low, and the prognosis of febrile seizures occurring shortly after vaccination was similar to the prognosis of febrile seizures occurring outside the risk period of vaccination. The DTaP-IPV-Hib vaccination was not associated with an increased risk for epilepsy.

Author Affiliations: Department of Public Health (Drs Sun, Li, Olsen, and Vestergaard) and Research Unit for General Practice (Drs Vedsted and Vestergaard), Aarhus University, Aarhus, Denmark; Departments of Neurology and Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark (Dr Christensen); Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (Dr Hviid); and Department of Epidemiology, School of Public Health, University of California, Los Angeles (Dr Olsen).

Author Contributions: Dr Sun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sun, Christensen, Hviid, Olsen, Vestergaard.
Acquisition of data: Li, Vedsted, Olsen, Vestergaard.
Analysis and interpretation of data: Sun, Christensen, Hviid, Li, Vedsted, Olsen, Vestergaard.
Drafting of the manuscript: Sun.
Critical revision of the manuscript for important intellectual content: Sun, Christensen, Hviid, Li, Vedsted, Olsen, Vestergaard.
Statistical analysis: Sun.
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