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

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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-

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