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

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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 vaccinaton, although the absolute risk was small. Vaccination with DTaP-IPV-Hib was not associated with an increased risk of epilepsy.

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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