Vaccine 32 (2014) 2574–2581

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort☆

Sara Y. Tartof*, Hung Fu Tseng, Amy L. Liu, Lei Qian, Lina S. Sy, Rulin C. Hechter, S. Michael Marcy, Steven J. Jacobsen

*Kaiser Permanente Southern California, Department of Research & Evaluation, USA*

ARTICLE INFO

*Article history:*
Received 25 November 2013
Received in revised form 3 March 2014
Accepted 13 March 2014
Available online 25 March 2014

*Keywords:*
Febrile convulsion
Febrile seizures
Vaccination
Risk factors
Interaction

ABSTRACT

*Introduction:* It is not known whether there are underlying physiologic or immunologic differences between febrile seizures (FS) triggered by vaccines versus other causes. Furthermore, while secular and individual-level factors have been associated with FS risk, they are rarely evaluated simultaneously.
*Methods:* Subjects included members of Kaiser Permanente Southern California aged 6 months to 3 years from July 1, 2003–December 31, 2011. Primary outcome was first diagnosis of FS. Vaccine-associated (VA) FS were defined as those occurring from day 0 to day 15 following any vaccine; non-vaccine associated (NVA) FS were those outside this period. We compared incidence rates of VA-FS versus NVA-FS. Poisson regression was used to assess the association between FS and secular and individual-level factors. We also evaluated interactions between vaccine exposure and each model covariate on the risk of FS.
*Results:* Among 265,275 children, 3348 FS were identified; 383(11%) were VA-FS, and 2965(89%) were NVA-FS. Incidence rates were 2.73 and 2.05 per 100,000 person-days for VA-FS and NVA-FS, respectively. Multivariable analyses confirmed previously reported increased risk of FS by age, low gestational age, and winter months. Increased risk was also associated with VA exposure (RR = 1.63[95% CI: 1.27–2.11]), non-White race/ethnicity vs. White (African-American RR = 1.41[1.22–1.63]; Asian RR = 1.58[1.40–1.79]; Hispanic RR = 1.60[1.47–1.75]), and maternal age 29 years or less vs. 40+ years (≤19 years RR = 1.28[1.00–1.65]; 20–29 years RR = 1.21[1.02–1.42]). Females were at lower risk of NVA-FS (RR = 0.77[0.72–0.83]), but were similar to males for VA-FS (RR = 0.97[0.79–1.19]). Children with low 1 min Apgar scores (≤3) had increased risk of VA-FS (RR = 3.40[1.86–6.22]), but no increased risk for NVA-FS (RR = 1.05[0.69–1.60]) compared to children with normal Apgar scores (≥7).
*Discussion:* This study suggests that there may be immunogenetic differences underlying VA-FSs compared with other FSs. However, further studies are needed. An understanding of the mechanisms behind these findings may help improve vaccine design or policies.



## 1. Introduction

While febrile seizures (FS) are generally not associated with high morbidity or mortality, they are the most common cause of pediatric seizures and are very frightening for parents [1–3]. FS frequently lead to emergency department (ED) admissions, and often recur in the children who suffer from them [4]. Simple febrile seizures are defined as brief (<15-min) generalized seizures that occur once during a 24-h period in a febrile child who does not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [2].

Several risk factors for FS have been identified. The peak incidence of FS occurs in the second year of life [2,5]. Febrile infections also play an important role in FS risk. Viral infections are very common in infants and young children and thus more frequently cause FS compared with bacterial infections. Certain viruses have been implicated more frequently than others [6–12]. As such, seasonal trends in the circulation of viral respiratory pathogens have been shown to coincide with seasonal variation in FS incidence [13–17].

☆ *CDC Disclaimer*: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author at: Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles, 2nd Floor, Pasadena, CA 91101, USA. Tel.: +1 626 564 3001; fax: +1 626 564 3694.

*E-mail addresses:* sara.y.tartof@kp.org, startof@gmail.com (S.Y. Tartof), Hung-fu.X.Tseng@kp.org (H.F. Tseng), Amy.L.Liu@kp.org (A.L. Liu), Lei.X.Qian@kp.org (L. Qian), lina.s.sy@kp.org (L.S. Sy), Rulin.C.Hechter@kp.org (R.C. Hechter), smmarcy@labiomed.org (S. Michael Marcy), steven.j.jacobsen@kp.org (S.J. Jacobsen).

http://dx.doi.org/10.1016/j.vaccine.2014.03.044
0264-410X/

Several vaccines have also been associated with elevated risk of FS, including whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP), measles-containing vaccines, some formulations of inactivated influenza vaccines, and the 13-valent pneumococcal conjugate vaccine (PCV13) [18–25]. There is a strong genetic component to FS risk which increases with a history of febrile seizure in first-degree relatives [26–30]. Finally, decreasing gestational age and low birth weight have also been previously identified as risk factors for FS [29].

Although season and calendar year as well as individual risk factors influence FS risk, their relative influence is not known as they are rarely if ever evaluated in the same analyses. Furthermore, it is not known if there are underlying physiologic or immunologic differences between FS triggered by different precipitating causes, such as vaccines versus other causes. In this study we used electronic medical records from a large, integrated 3.6 million-member managed care organization to compare incidence rates of vaccine-associated (VA) and non-vaccine associated (NVA) FS and to evaluate whether temporal and individual risk factors differ for VA and NVA-FS.

## 2. Methods

### 2.1. Source population

The study included members of Kaiser Permanente Southern California (KPSC) healthcare system. KPSC consists of 3.6 million members who are representative of the socioeconomic and racial diversity of the area population [31]. KPSC uses electronic medical records (EMR) to integrate medical information from all outpatient, ED, and hospital settings. When care is received from non-KPSC providers, visit details are captured through claims required for reimbursement; claims data were included in this study. Vaccinations received by members are tracked in the EMR, regardless of whether they are administered in or outside of KPSC.

### 2.2. Study population

The study cohort consisted of all children 6 months up to 3 years of age (i.e. through 2.99 years) from July 1, 2003 through December 31, 2011, with continuous membership coverage from birth to censorship (end of membership, 3 years age, end of study, first development of FS). A 31 day gap in membership was permitted from 6 months to 3 years, and a 61 day gap in membership was permitted for ages 0–6 months (the longer gap accounts for common time lag for newborns to be enrolled in insurance plan). The protocol for this study was reviewed and approved by the KPSC institutional review board, which waived requirement for informed consent.

### 2.3. Outcome of interest

Children with a first diagnosis of FS on or after age 6 months up to 3 years of age from July 1, 2003 through December 31, 2011 were identified among the cohort members. A diagnosis of FS was determined based on International Classification of Diseases Ninth Revision (ICD-9) codes (ICD-9 780.31, 780.32) identified in either the inpatient and ED settings. Prior work in the Vaccine Safety Datalink (VSD) consortium has demonstrated a high positive predictive value for FS following vaccination in these settings combined [25,32].

Exclusion criteria were applied from birth and included seizures with fever in children who had previous evidence of intracranial infection, history of afebrile seizures, metabolic disturbances, previous neurologic insults, or known to have central nervous system abnormalities. Determination of exclusion criteria were based on ICD-9 codes (Appendix 1) and was made using inpatient, ED, and outpatient files.

### 2.4. Exposure of interest

VA-FS were defined as those that occurred from day 0 (day of vaccine administration) to day 15 following receipt of any vaccines recommended by the Advisory Committee on Immunization Practices for use in children aged 6 months up to 3 years of age. NVA-FS were defined as all other FS occurring outside the 0–15 day follow-up period post-vaccination. For vaccines administered during overlapping periods (i.e. more than one vaccine in the 0–15 day risk period), the follow-up period began when the first vaccine was administered and ended 15 days following receipt of the final vaccine in the overlapping period.

### 2.5. Additional variables of interest

Individual level risk factors including self-reported race/ethnicity, sex, birth weight, gestational age, mother's age, and 1 and 5-min Apgar scores were collected. Age was calculated on the first day of every month and was modeled as a time-varying confounder. For all FS cases, age at onset of first FS, and calendar year and season of onset of FS were collected.

### 2.6. Vaccine subgroups

For exploratory purposes, all vaccinations were categorized into four subgroups (bacterial, viral, measles-mumps-rubella [MMR], or diphtheria-tetanus-acellular pertussis [DTaP]) based on vaccine contents (Appendix 2). The bacterial and viral subgroups consisted of vaccines targeted against bacteria and viruses, respectively; the DTaP subgroup included vaccines with any DTaP components; the MMR subgroup included vaccines with MMR components. DTaP-containing vaccines were excluded from the bacterial subgroup; MMR-containing vaccines were excluded from the viral subgroup. Study members could be categorized as having multiple subgroups on a single day. Combination vaccines with viral and bacterial components (HepB/Hib) were included in the viral and bacterial subgroups; those with DTaP-containing and viral components were included in the DTaP and viral subgroups (DTaP/IPV; DTaP/HepB/IPV; DTaP/Hib/IPV).

### 2.7. Statistical analyses

Monthly and annual incidence rates for VA and NVA-FS were calculated during the study period from July 1, 2003 to December 31, 2011 using person-time denominators. For incidence rates, 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of FS cases. Overall estimates for the study period were calculated as total FS cases divided by total person-time during the study period. Incidence estimates and 95% CIs were also stratified by vaccine subgroup.

Bivariate analyses between FS outcome and covariates were conducted to assess potential confounders for inclusion in the multivariate model. Subsequently, a Poisson regression model was used to assess the effect of temporal trends (annual and monthly) and individual level risk factors (vaccine exposure, age at FS onset, race/ethnicity, sex, birth weight, gestational age, 1 and 5 min Apgar score), on risk of FS. In order to assess whether the levels of risk of any of the variables in the model differed between VA and NVA exposure time, we modeled each covariate in the multivariate model as an interaction term with the 'vaccine' term to test for statistical significance. All analyses were conducted using SAS v9.2 (SAS Institute Inc., Cary, North Carolina).