

# **Febrile Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) Study**

**Advisory Committee on Immunization Practices  
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## **Febrile Seizure**

- **The American Academy of Pediatrics defines febrile seizures as, “seizures that occur in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures.”**

## Vaccines Previously Associated with an Increased Risk of Febrile Seizure

Vaccine	Post-vaccination risk interval, days
Diphtheria-Tetanus-whole cell Pertussis (DTP)	0 – 3
Measles-Mumps-Rubella (MMR)	6 – 11
Measles-Mumps-Rubella-Varicella (MMRV)	7 – 10
Inactivated Influenza (TIV) 2010-2011 season formulation	0 – 1
Pneumococcal conjugate vaccine-13 valent (PCV13)	0 – 1

## **Febrile Seizures After TIV and PCV13**

- **Australia, 2010**
  - Risk of febrile seizure in the first 24 hours after TIV
- **VSD Influenza Rapid Cycle Analysis (RCA) for 2010-2011**
  - Risk of febrile seizure on days 0-1 after TIV
  - Concomitant TIV and PCV13 had a higher risk of febrile seizure than either vaccine given separately
  - Risk of febrile seizure on days 0-1 after PCV13
- **VSD PCV13 RCA**
  - No increased risk of febrile seizure compared to PCV7

## Objective

- To assess whether vaccines other than PCV13 given concomitantly with TIV affect the risk of febrile seizure following receipt of TIV.

## Methods

- The Vaccine Safety Datalink (VSD) is a collaboration between CDC and several integrated health care organizations.
- VSD has a combined annual population of over nine million people (~ 3% of US population).

# VSD Sites Contributing Data to this Study



## Methods

- **Case-finding**
  - Medical visits with ICD-9 diagnosis code 780.3x (convulsion)
  - Occurring in the ED or inpatient settings
  - First occurrence in 42 days
- **Case-confirmation**
  - Medical records were abstracted to confirm the diagnosis and the time of onset in relation to vaccination
- **Study period:** July 1, 2006 to July 1, 2011
- **Ages:** 6 through 23 months



## **Febrile Seizure Case Definition**

- **Clinician diagnosis of seizure, and**
- **fever measured or reported, and**
- **excluding patients with intracranial infection, metabolic disturbance, or history of afebrile seizures.**

# Analysis

- **Self-Controlled Risk Interval (SCRI) method**
  - Conditional Poisson regression models the Incidence Rate Ratio (IRR)
  - Only uses cases that occur post-vaccination
    - Risk interval: days 0 – 1
    - Comparison interval: days 14 – 20



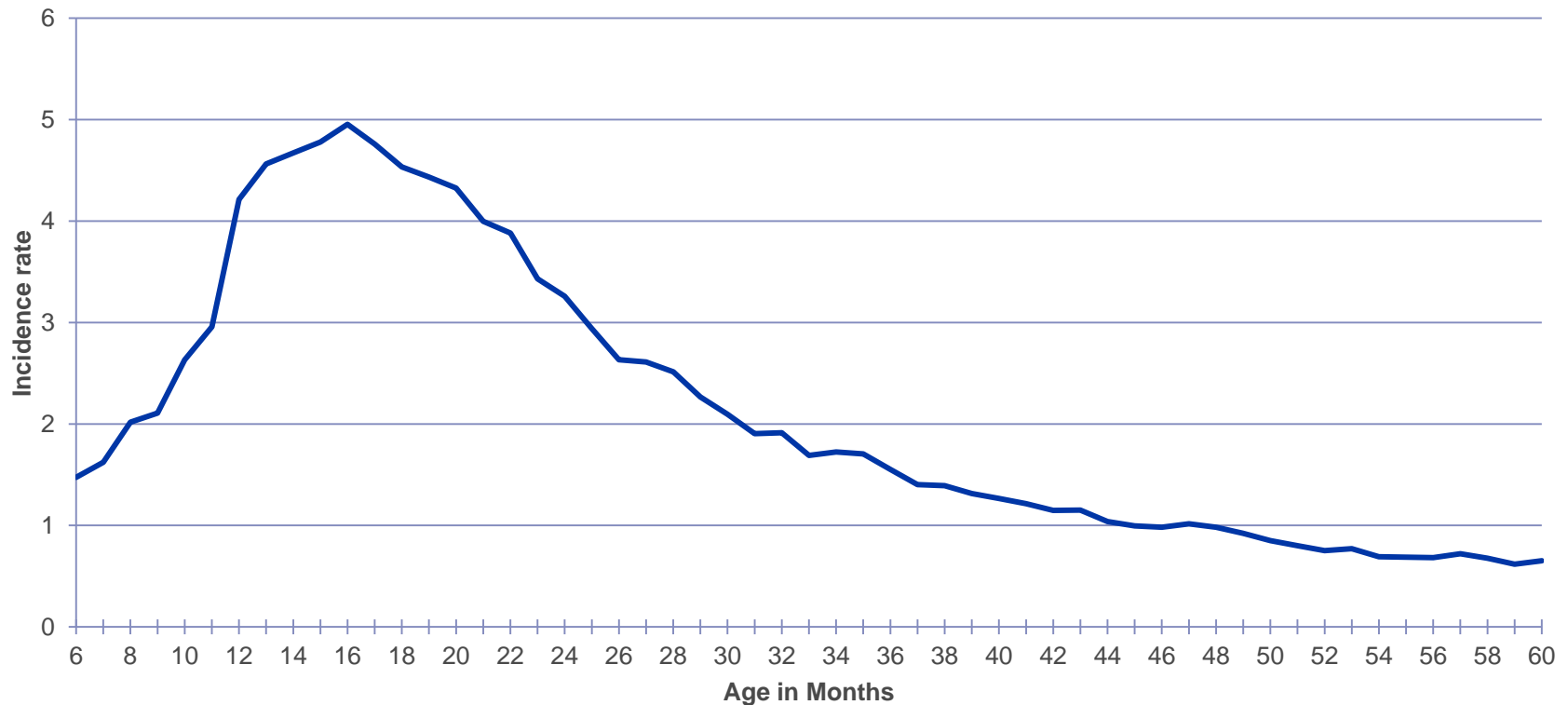
## Attributable Risk Estimate

- Estimated as:  $(IRR - 1) * \text{background incidence rate in the VSD population per person day} * 2 \text{ person days}$

# **RESULTS: ADMINISTRATIVE DATA**

# VSD Population Febrile Seizure Background Rate

Incidence rate per 100,000 person days by age in months



Based on ICD-9 coded data

## Number of unique vaccine combinations received by children in the VSD, 2000-2011

Age group (months)	Unique combinations (n)
6 – 11	1,582
12 – 23	2,707

## Vaccine doses given at ages 6-23 months

Vaccine	Total Doses	Doses Given Alone	Percent Given Alone
HepB	221,179	43,282	20%
RV5	285,456	1,528	1%
DTaP	1,079,684	98,004	9%
DTaP-IPV-HepB	583,994	14,545	2%
DTaP-IPV-Hib	73,070	2,080	3%
Hib	1,152,710	25,826	2%
Hib-HepB	145,784	2,416	2%
PCV7	1,496,120	65,862	4%
PCV13	218,732	7,152	3%
IPV	308,067	16,633	5%
TIV	955,720	484,454	51%
MIV	108,526	48,482	45%
MMR	725,392	15,935	2%
VAR	700,650	18,038	3%
MMRV	168,616	4,431	3%
HepA	650,139	140,040	22%

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## TIV doses by flu season

Flu Season	Total TIV doses	TIV doses alone	TIV alone	TIV with MIV* only
2006-07	123,034	65,392	53%	-
2007-08	125,716	64,533	51%	-
2008-09	132,300	66,996	51%	-
2009-10	145,249	54,011	37%	53%
2010-11	155,544	71,372	46%	-

\*MIV= Influenza A(H1N1)pdm2009 monovalent inactivated vaccine

## SCRI analysis of TIV by flu season using non-chart-confirmed data

	TIV alone	TIV with other vaccines
Flu Season	IRR (95% CI)	IRR (95% CI)
2006-07	0.21 (0.03-1.55)	4.90 (2.18-11.03)
2007-08	0.22 (0.03-1.65)	0.95 (0.27-3.42)
2008-09	0.88 (0.25-3.10)	4.14 (1.85-9.23)
2009-10	0.35 (0.08-1.50)	1.93 (0.92-4.02)
2010-11	2.19 (0.72-6.69)	3.83 (2.12-6.93)

# **RESULTS: CHART-CONFIRMED DATA**

## Case-finding

Vaccination visits (ages 6-23 months, 2006-07 through 2010-11 flu seasons)

1,915,108



Medical visits with convulsion ICD-9 code during the post-vaccination intervals

Total: 596

Risk (days 0-1): 183

Comparison (days 14-20): 413



Charts Requested (random sample)

468



Charts Available

428

## Febrile Seizure Chart Confirmation

Exclusion reason	Number excluded	Running Total (n=428)
Case definition related		
Not a new seizure event	18	410
“Possible seizure”	14	396
Non-febrile seizure	21	375
Fever status not documented	27	348
Exposure related		
Vaccinated after seizure	2	346
Seizure not in SCRI intervals	11	335
Overlapping risk windows	2	333

**Chart-confirmed febrile seizures, n=333**

## Patient Characteristics

	Risk (n=103) %	Comparison (n=230) %	<i>P</i>
Age group (months)			.06
6-11	25	17	
12-23	75	83	
Sex			.21
Male	51	58	
Race			NS
AI/AN	4	2	
Asian	15	17	
Black	17	11	
White	39	37	
Other	32	29	
Unknown	10	17	
Ethnicity			.60
Hispanic	34	36	

## Patient Medical History

	Risk (n=103) %	Comparison (n=230) %	<i>P</i>
First seizure ever	52	49	.80
Family history	18	14	.40
Hx of premature birth	11	8	.40
Hx of NICU admission	11	7	.34
Hx of developmental delay	15	13	.88
Antipyretic previous 7 days	52	38	.01
Antibiotic previous 7 days	8	6	.57
Potential non-vaccine cause of fever present	37	77	< .0001
Admitted for the seizure	13	10	.88

## Patient Vaccine Exposures

Vaccine	Risk %	Comparison %	SCRI bivariate IRR (95% CI)
PCV7	51	30	2.7 (1.9 - 3.8)
Hib	46	25	2.9 (1.9 - 4.2)
TIV	43	37	1.8 (1.3 - 2.6)
HepA	43	45	1.5 (1.0 - 2.1)
DTaP	39	27	2.2 (1.5 - 3.3)
MMR	24	22	1.8 (1.1 - 2.8)
Var	24	22	1.7 (1.1 - 2.8)
DTaP-IPV-HepB	21	8	4.1 (2.2 - 7.5)
PCV13	17	10	2.6 (1.4 - 4.8)
RV5	13	5	3.8 (1.7 - 8.3)
MMRV	12	8	2.2 (1.1 - 4.6)
DTaP-IPV-Hib	5	5	1.5 (0.5 - 4.1)
HepB	4	3	2.0 (0.6 - 6.8)
MIV	3	8	0.6 (0.2 - 1.9)
IPV	1	0.5	3.5 (0.2 - 55)
PPV23	1	0	Undefined



## Vaccine Exposure Combinations

- Among the 333 cases, there were 129 unique vaccine combinations received.
- Among these combinations, only 21 were received by  $\geq$  four patients.

## Regression Modeling

- **First examined two time periods separately:**
  - 2006-07 through 2009-10 flu seasons
  - 2010-11 flu season
- **Then all study time pooled together**
- **Multivariate model building**
  - To identify vaccines associated with an increased risk of febrile seizure while accounting for confounding and effect modification between vaccines
  - Start with all vaccines in the model
  - Manual backward elimination process
  - With TIV as the main effect of interest

## **Regression Modeling continued**

- **Vaccines retained in the final multivariate model:**
  - TIV, PCV, DTaP-containing
- **Then also examined separate models for each strata defined by the mutually exclusive combinations of these three vaccines**

## 2006-07 – 2009-10 Flu Seasons

### SCRI Models for Strata defined by Combinations of Three Vaccines: TIV, PCV, DTaP-containing

Stratum	Vaccine(s) Received			n	IRR (95% CI)
1	TIV	-	-	52	0.4 (0.1 – 0.9)
2	-	PCV	-	36	2.0 (1.0 – 3.9)
3	-	-	DTaP-containing	32	1.4 (0.6 – 3.0)
4	-	PCV	DTaP-containing	55	2.2 (1.3 – 3.7)
5	TIV	-	DTaP-containing	16	3.5 (1.3 – 9.3)
6	TIV	PCV	-	6	3.5 (0.7 – 17)
7	TIV	PCV	DTaP-containing	23	6.6 (2.8 – 15)

## 2010-2011 Flu Season

### SCRI Models for Strata defined by Combinations of Three Vaccines: TIV, PCV, DTaP-containing

Stratum	Vaccine(s) Received			n	IRR (95% CI)
1	TIV	-	-	8	1.2 (0.2 – 5.8)
2	-	PCV	-	7	1.4 (0.3 – 7.2)
3	-	-	DTaP-containing	6	0.7 (0.1 – 6.0)
4	-	PCV	DTaP-containing	12	2.5 (0.8 – 7.9)
5	TIV	-	DTaP-containing	6	3.5 (0.7 - 17)
6	TIV	PCV	-	6	3.5 (0.7 - 17)
7	TIV	PCV	DTaP-containing	11	2.9 (0.9 – 9.6)

## All Flu Seasons

### SCRI Models for Strata defined by Combinations of Three Vaccines: TIV, PCV, DTaP-containing

Stratum	Vaccine(s) Received			2006-2009 n=267 IRR (95% CI)	2010-2011 n=66 IRR (95% CI)	2006-2011 n=333 IRR (95% CI)
1	TIV	-	-	0.4 (0.1 – 0.9)	1.2 (0.2 – 5.8)	0.5 (0.2 – 1.0)
2	-	PCV	-	2.0 (1.0 – 3.9)	1.4 (0.3 – 7.2)	1.8 (0.97 – 3.4)
3	-	-	DTaP- containing	1.4 (0.6 – 3.0)	0.7 (0.1 – 6.0)	1 (0.5 – 2.3)
4	-	PCV	DTaP- containing	2.2 (1.3 – 3.7)	2.5 (0.8 – 7.9)	2.3 (1.4 – 3.8)
5	TIV	-	DTaP- containing	3.5 (1.3 – 9.3)	3.5 (0.7 - 17)	3.5 (1.5 – 8.1)
6	TIV	PCV	-	3.5 (0.7 – 17)	3.5 (0.7 - 17)	3.5 (1.1 – 11)
7	TIV	PCV	DTaP- containing	6.6 (2.8 – 15)	2.9 (0.9 – 9.6)	5 (2.5 – 9.9)

## Attributable Risk (AR) Estimates for Combinations of Three Vaccines: TIV, PCV, DTaP-containing

	Vaccine(s) Received			IRR (95% CI)	AR* at 6 months	AR* at 12 months	AR* at 15 months
1	TIV	-	-	0.5 (0.2 – 1.0)	n/a	n/a	n/a
2	-	PCV	-	1.8 (0.97 – 3.4)	n/a	n/a	n/a
3	-	-	DTaP-containing	1 (0.5 – 2.3)	n/a	n/a	n/a
4	-	PCV	DTaP-containing	2.3 (1.4 – 3.8)	3	8	12
5	TIV	-	DTaP-containing	3.5 (1.5 – 8.1)	6	15	24
6	TIV	PCV	-	3.5 (1.1 – 11)	6	15	24
7	TIV	PCV	DTaP-containing	5 (2.5 – 9.9)	10	24	38

\* per 100,000 persons vaccinated; compared to the background rate.

- n/a: AR not calculated when IRR is not statistically significant.

## Conclusions

- The concomitant administration of TIV + PCV and TIV + DTaP-containing vaccines had higher risks of febrile seizure than when the vaccines were given independently.
- The concomitant administration of TIV + PCV + DTaP-containing vaccines had the highest risk.
- These increased risks with concomitant vaccination were observed in all influenza seasons studied, not just during the 2010-11 season.



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