No association of incident epilepsy with up-to-date vaccination status or vaccine aluminum exposure in children less than 48 months of age (VSD Study # 1330)

David L. McClure, PhD[1] • Kayla E. Hanson, MPH[1] • James G. Donahue, PhD[1] • Burney A. Kieke, MS[1] • Jonathan Duffy, MD, MPH[2] • Michael M. McNeil, MD[2] • Jason M. Glanz, PhD[3]
Stephanie Irving, MHS[4] • Elyse O. Kharbanda, MD, MPH[5] • Joshua T.B. Williams, MD[6] • Stanley Xu, PhD[7] • Ousseny Zerbo, PhD[8] • Jennifer C. Nelson, PhD[9] • Edward A. Belongia, MD[1]

[1]Marshfield Clinic Research Institute, Marshfield, WI • [2]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA
[3]Kaiser Permanente Institute for Health Research, Denver, CO • [4]Kaiser Permanente Center for Health Research, Portland, OR • [5]HealthPartners Institute, Minneapolis, MN
[6]Denver Health and Hospitals, Denver, CO • [7]Kaiser Permanente Department of Research and Evaluation, Pasadena, CA • [8]Kaiser Permanente Vaccine Study Center, Oakland, CA
[9]Kaiser Permanente Washington Health Research Institute, Seattle, WA

David McClure
McClure.David
@marshfieldresearch.org

Background

- No vaccine safety study of epilepsy on the childhood vaccination schedule has yet been published
- A 2013 Institute of Medicine report noted the literature is "limited and inconclusive" and 11 years later it still is

Objectives

Perform a case-control study to assess the association between incident epilepsy among children <48 months of age and:
- up-to-date vaccination status
- cumulative aluminum exposures

Methods

Study Design and Population
- Matched case-control study nested within VSD early childhood cohort (Cycle 2018)
- Children up to age 48 months in 2008 through 2018 and born in VSD cohort with continuous enrollment through 24 months of age and met well child visit (≥ 2 before 12 months and ≥1 from 12 to 23 months of age) and no vaccine contraindication criteria

Cases
- Identified using ICD-9-CM and ICD-10-CM codes, and antiepileptic Rx's following a published step-wise algorithm

Controls
- Selected from study population not having any diagnostic codes for epilepsy/afebrile seizures or records of antiepileptic Rx's

Matching
- Cases matched to up to 10 controls on index date (distinct case date), age (birthdate ±2 weeks), sex, and VSD participating site

Exposures
- Based on ACIP recommended vaccine doses received before the index date
- Primary: dichotomous up-to-date vaccination status
- Secondary: cumulative aluminum content in mg from vaccination

Results

Case and Control Characteristics

Variable	Cases No. (%)	Controls No. (%)	Variable	Cases No. (%)	Controls No. (%)
Age 1 to 23 Months	1271 (68.6%)	12462 (69.6%)	Medicaid	302 (16.3%)	2021 (11.3%)
Age 24 to 47 Months	581 (31.4%)	5456 (30.4%)	Race/Ethnicity		
Males	1009 (54.5%)	9725 (54.3%)	White Non-Hisp.	711 (41.6%)	7400 (41.3%)
Preterm Birth	224 (12.1%)	1375 (7.7%)	White Hispanic	539 (29.1%)	4942 (27.6%)
Family Hx Epilepsy	43 (2.3%)	15 (0.1%)	Asian	223 (12.0%)	4942 (27.6%)
Renal Disease	25 (1.3%)	63 (0.4%)	Black	132 (7.1%)	2574 (14.4%)
Epilepsy Risk Factors	411 (22.2%)	893 (5.0%)	Other Races/Ethnicities	77 (4.2%)	656 (3.7%)
Parenteral Nutrition	101 (5.5%)	334 (1.9%)	Missing	91 (4.9%)	1209 (6.7%)

Epilepsy risk factors were various genetic, metabolic, structural (brain injuries or malformations) conditions and encephalitis or meningitis infections.

Primary Analysis: Adjusted Odds Ratios

Effect	Odds Ratio (95% CL)	P-value
Up-to-Date Status	**0.89 (0.79 - 1.00)**	**0.0445**
Preterm Birth	1.24 (1.04 - 1.49)	0.0169
Family Hx Epilepsy	25.7 (14.0 - 47.1)	<0.0001
Epilepsy Risk Factors	5.29 (4.61 - 6.07)	<0.0001
Parenteral Nutrition	1.91 (1.45 - 2.53)	<0.0001
Renal Disease	2.76 (1.66 - 4.57)	0.0001
Medicaid	1.58 (1.34 - 1.87)	<0.0001

Effect	Odds Ratio (95% CL)	P-value
Aluminum per mg	**0.98 (0.90 - 1.07)**	**0.7142**
Preterm Birth	1.27 (1.06 - 1.51)	0.0169
Family Hx Epilepsy	24.8 (13.6 - 45.5)	<0.0001
Epilepsy Risk Factors	5.41 (4.72 - 6.20)	<0.0001
Parenteral Nutrition	1.99 (1.51 - 2.63)	<0.0001
Renal Disease	2.80 (1.69 - 4.63)	0.0001
Medicaid	1.59 (1.34 - 1.87)	<0.0001

Race/ethnicity adjusted odds ratios (95% CL) were nearly identical for either analysis. Shown for up-to-date and vs. WNH : Asian 0.9 (0.8-1.0), Black 1.3 (1.1-1.6), Native Hawaiian or Pacific Islander 1.0 (0.6-1.9), White Hispanic 1.1 (0.9-1.2), American Indian or Alaska Native 0.9 (0.4-2.4), other races/ethnicities 1.1 (0.9-1.5), missing 0.7 (0.6-0.9).

Abbreviations: CL = confidence limit, Hx = medical history, WNH = White Non-Hispanic

Secondary Analysis: Adjusted Odds Ratios

Effect	Odds Ratio (95% CL)	P-value
Age 1 to 23 Months		
Up-to-Date Status	0.86 (0.75 - 1.00)	0.0419
Age 24 to 47 Months		
Up-to-Date Status	0.95 (0.76 - 1.18)	0.6247
Without Epilepsy Risk Factors		
Up-to-Date Status	0.94 (0.82 - 1.07)	0.4093

Effect	Odds Ratio (95% CL)	P-value
Age 1 to 23 Months		
Aluminum per mg	0.99 (0.89 - 1.10)	0.8271
Age 24 to 47 Months		
Aluminum per mg	0.95 (0.84 - 1.13)	0.6986
Without Epilepsy Risk Factors		
Aluminum per mg	1.04 (0.94 - 1.15)	0.4327

Age stratified and without epilepsy risk factors analyses were adjusted for preterm birth, family history of epilepsy, renal disease, parenteral nutrition, Medicaid status, and race/ethnicity. Age stratified analysis were also adjusted for epilepsy risk factors.

Statistical Methods

- Conditional Logistic Regression – conditioning on matched strata and adjusted odds ratios with inclusion of possible *a priori* confounders
- Primary Analyses – two overall models:
  - Separate models for up-to-date and aluminum exposure
- Secondary Analyses
  - Two age-stratified models – 1 through 23 months and 24 through 47 months
  - One model restricted to cases with epilepsy risk factors and their matched controls

Summary of Major Findings

- Up-to-date vaccination (UTDV) was associated with slightly reduced odds of epilepsy overall
- UTDV was associated with reduced odds of epilepsy in children <24 months of age but not in older children
- Aluminum exposure (AL) was not associated with epilepsy overall
- No association with AL by age group
- No association for UTDV or AL among children without epilepsy risk factors

Limitations

- Retrospective, data-only study without medical record reviews of exposures, confounders, or outcomes
- The VSD study cohort is <5% of the age-eligible U.S. population

Conclusions

For children less than 48 months of age, vaccines are safe with respect to incident epilepsy and cumulative aluminum exposure

Acknowledgements