Vaccines Are Not Associated With Metabolic Events in Children With Urea Cycle Disorders

AUTHORS: Thomas M. Morgan, MD,^{a,b,c} Cameron Schlegel, BA,^c Kathryn M. Edwards, MD,^{a,c} Teresa Welch-Burke, RN, BSN, CCRP,^{a,c} Yuwei Zhu, MD, MS,^c Robert Sparks, BA,^{a,c} Marshall Summar, MD,^{b,c,d} and the Urea Cycle Disorders Consortium

^aDepartment of Pediatrics and ^bCenter for Human Genetics Research, ^cDepartment of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee; and ^dDivision of Genetics and Metabolism and Center for Genetic Medicine Research, Children's National Medical Center, Washington, DC

KEY WORDS

vaccine risk, safety, inborn error of metabolism, urea cycle, hyperammonemia, encephalopathy

ABBREVIATIONS

IEM—*inborn error(s) of metabolism*
UCD—*urea cycle disorder*
HAE—*hyperammonemic episode*
HepB—*hepatitis B*
SCCS—*self-controlled case series*
UCDC—*Urea Cycle Disorders Consortium*

Dr Morgan and Ms Schlegel contributed equally to this work.

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Address correspondence to Thomas M. Morgan, MD, Department of Pediatrics/Division of Genetics and Genomic Medicine, Vanderbilt University School of Medicine, DD-2205 Medical Center North, Nashville, TN 37232-2578. E-mail: thomas.morgan@vanderbilt.edu

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WHAT'S KNOWN ON THIS SUBJECT: There have been no large controlled studies on vaccine safety in the vulnerable population of children with urea cycle disorders.

WHAT THIS STUDY ADDS: The results provide substantial reassurance of the safety of vaccinations in medically fragile children with urea cycle disorders.

abstract

BACKGROUND: Despite the success of childhood immunizations in prevention of infectious diseases, questions remain about the safety of vaccines in medically fragile children with inborn errors of metabolism such as urea cycle disorders (UCDs). Patients with UCDs are subject to hyperammonemic episodes (HAEs) after infection, fever, or other stressors.

OBJECTIVE: We sought to assess the risk of HAEs that required urgent care or hospitalization after routine vaccinations in pediatric patients with underlying UCDs.

METHODS: This was a retrospective investigation of vaccine safety in children with UCDs within the longitudinal Rare Diseases Clinical Research Consortium for UCD. Postvaccination exposure periods were defined as 7 or 21 days after any immunization. The association of vaccines and HAEs was modeled by using conditional Poisson regression, adjusting for age, and using a self-controlled case series method including all patients with ≥ 1 HAE and with any vaccine exposure.

RESULTS: The study enrolled 169 children younger than 18 years. Of these children, 74 had records of at least 1 HAE and at least 1 vaccination. With adjustment for age, there was no increase in relative incidence of HAEs in either the 7-day (1.31 [95% confidence interval (CI): 0.80–2.13]) or 21-day (1.05 [95% CI: 0.74–1.47]) exposure period after vaccination compared with HAEs outside of the vaccination periods. No vaccine type was associated with significantly more HAEs.

CONCLUSIONS: We found no statistically significant association between childhood immunizations and HAEs in children with UCDs. The results support the safety of immunization in this medically vulnerable population. *Pediatrics* 2011;127:e1147–e1153

Inborn errors of metabolism (IEM) are a group of genetic conditions resulting in derangement of synthesis, transport, or disposal of vital molecules, including carbohydrates, fats, and proteins. Urea cycle disorders (UCDs), a specific subtype of IEM with a collective incidence of 1 in 44 000 births,^{1,2} are caused by mutations in any of 6 enzymes or 2 mitochondrial transporters in the urea cycle.³ The most extreme forms of UCD result from absence of any of the first 5 enzymes: ornithine transcarbamylase deficiency (most common); carbamoyl phosphate synthetase I deficiency; argininosuccinic acid synthetase deficiency or citrullinemia; argininosuccinic acid lyase deficiency or argininosuccinic aciduria; and *N*-acetylglutamate synthetase deficiency.³ Initial UCD symptoms typically occur on neonatal catabolism and exposure to milk protein, and include poor feeding, hypothermia, and somnolence, progressing to hypoventilation or hyperventilation, seizures, dystonic posturing, and, ultimately, coma.^{4–6} Diagnosis is strongly suggested by documenting plasma ammonia levels of $>150\ \mu\text{mol/L}$, normal anion gap, and normal serum glucose, and definitive confirmation is made with additional genetic or enzymatic evaluation.⁷ Expanded newborn screening using tandem mass spectrometry for elevated citrulline levels detects patients with argininosuccinic acid synthetase and argininosuccinic acid lyase deficiencies (although results may be too late to aid in treatment of severe cases); most importantly, however, it does not detect other UCDs, including the most common, ornithine transcarbamylase deficiency.⁸

Despite early diagnosis and appropriate treatment with protein restriction and ammonia-scavenging agents, patients with UCD typically experience recurrent hyperammonemic episodes

(HAEs) during periods of excessive protein intake or catabolic stress. Therefore, children with UCD are at high risk of devastating metabolic decompensation in the setting of acute childhood illnesses, including vaccine-preventable diseases.^{9,10} Immunizations may mimic infections, causing similar, typically milder inflammatory and metabolic responses. The safety of vaccines in children with UCDs has not been systematically investigated.⁸ The Centers for Disease Control and Prevention has made no special recommendations regarding immunization of patients with IEM.¹¹ In the *2009 Red Book*, the American Academy of Pediatrics Committee on Infectious Diseases recommends that patients with IEM receive standard immunizations and additional “referral to a specialist for guidance.”¹² Although metabolic experts support routine immunization in children with UCD and other IEMs, few studies have investigated whether adverse events after vaccination are more common in this population.^{9,13}

Concern about vaccine safety has arisen from limited case reports suggesting that vaccination may be sufficient to trigger a metabolic crisis in children with IEM.^{14,15} Because of the metabolic vulnerability of children with UCDs, our goal was to assess the risk of HAEs resulting in subsequent medical care after routine vaccinations of pediatric patients with underlying UCDs.

METHODS

Study Population

Patients were participants in the longitudinal National Institutes of Health-sponsored Rare Diseases Clinical Research Consortium for UCD (RR19453).⁸ At enrollment, data were abstracted retrospectively from medical records (patient enrollment dates from February 6, 2006, to July 31, 2009; charts were reviewed up to 18 years

before enrollment) and then updated at comprehensive follow-up visits every 3 months until 2 years of age, or every 6 months for patients older than 2 years of age. The clinical data set included all hospitalizations and urgent care for symptomatic HAE along with dates of vaccination. On UCD diagnosis and subsequent referral to pediatric specialty centers (as shown in Table 1), clinical information dating from birth was obtained, including vaccination data. Children were observed from birth, as care of patients with UCD is highly centralized and coordinated by a small group of clinical geneticists. Inclusion criteria were age at enrollment from newborn up to 18 years of age, and all UCD diagnoses were eligible, including *N*-acetylglutamate synthetase deficiency; carbamoyl phosphate synthetase I deficiency; ornithine transcarbamylase deficiency; argininosuccinic acid synthetase deficiency; argininosuccinic acid lyase deficiency or argininosuccinic aciduria; arginase deficiency; and citrin and ornithine transporter defects.^{3,7} Asymptomatic heterozygous females ascertained through diagnosis of an affected family member were excluded. Patients could self-refer through the Rare Diseases Clinical Research Network (published by the National Institutes of Health) or be referred by a medical care provider, a prenatal diagnostic center, or the National Urea Cycle Disorders Foundation.

Study Design

This was a retrospective, analytical study of patients diagnosed with UCD, focusing on those experiencing at least 1 vaccination and 1 episode of HAE. HAEs were defined as those episodes associated with plasma ammonia levels of $>150\ \mu\text{mol/L}$ and requiring a hospitalization, emergency department, or urgent care visit.⁷ The incidence of HAEs within 7- and/or 21-day postvaccination periods (day of

TABLE 1 Characteristics of Patients With or Without HAEs After Vaccination Exposure

	No Vaccine Records (N = 57)	Vaccination Records Obtainable			All (N = 169)
		No HAEs (N = 38)	≥1 HAE (N = 74)	All (N = 112)	
Gender, % (n)					
Female	58 (33)	63 (24)	51 (38)	55 (62)	56 (95)
Male	42 (24)	37 (14)	49 (36)	45 (50)	44 (74)
HAE at <30 d of age, % (n)					
No	53 (30)	100 (38)	43 (32)	62 (70)	59 (100)
Yes	46 (26)	0 (0)	57 (42)	38 (42)	40 (68)
Unknown	2 (1)	0 (0)	0 (0)	0 (0)	1 (1)
UCD subdiagnosis, % (n)					
ALD	19 (11)	29 (11)	18 (13)	21 (24)	21 (35)
ARGD	4 (2)	5 (2)	4 (3)	4 (5)	4 (7)
ASD	18 (10)	34 (13)	19 (14)	24 (27)	22 (37)
CITRD	0 (0)	3 (1)	1 (1)	2 (2)	1 (2)
CPSID	4 (2)	0 (0)	4 (3)	3 (3)	3 (5)
ORNT1	2 (1)	0 (0)	3 (2)	2 (2)	2 (3)
OTCD	44 (25)	26 (10)	42 (31)	37 (41)	39 (66)
Undefined UCD	11 (6)	3 (1)	9 (7)	7 (8)	8 (14)
Institution, % (n)					
Baylor College of Medicine (UCDC)	19 (11)	16 (6)	15 (11)	15 (17)	17 (28)
Children's Hospital Boston (UCDC)	2 (1)	3 (1)	4 (3)	4 (4)	3 (5)
Children's Hospital of Philadelphia	2 (1)	24 (9)	3 (2)	10 (11)	7 (12)
Children's National Medical Center	14 (8)	8 (3)	27 (20)	21 (23)	18 (31)
Rainbow Babies & Children's Hospital	7 (4)	5 (2)	4 (3)	4 (5)	5 (9)
Mt Sinai Hospital (UCDC)	11 (6)	3 (1)	12 (9)	9 (10)	9 (16)
Oregon Health & Science University (UCDC)	2 (1)	0 (0)	1 (1)	1 (1)	1 (2)
Seattle Children's Hospital	4 (2)	0 (0)	3 (2)	2 (2)	2 (4)
Children's Hospital, Colorado (UCDC)	2 (1)	5 (2)	4 (3)	4 (5)	4 (6)
Hospital for Sick Children (UCDC)	7 (4)	0 (0)	0 (0)	0 (0)	2 (4)
University Children's Hospital Zurich	12 (7)	8 (3)	4 (3)	5 (6)	8 (13)
University of California at Los Angeles (UCDC)	7 (4)	5 (2)	7 (5)	6 (7)	7 (11)
Vanderbilt University Medical Center	11 (6)	18 (7)	12 (9)	14 (16)	13 (22)
Yale University School of Medicine	2 (1)	5 (2)	4 (3)	4 (5)	4 (6)
Age as of July 31, 2009, 25th/50th/75th percentiles	5/11/16	4/7/11	3/7/11	3/7/11	4/9/13
Age as of July 31, 2009, mean (SD), y	10.9 (6.5)	7.8 (4.7)	7.4 (5.0)	7.5 (4.8)	8.7 (5.7)
Age at enrollment, 25th/50th/75th percentiles	3/9/14	1/6/10	1/5/9	1/5/9	2/6/10
Age at enrollment, mean (SD), y	8.9 (6.2)	5.9 (4.4)	5.6 (4.8)	5.7 (4.7)	6.8 (5.5)

ALD indicates ALD (argininosuccinic acid lyase deficiency); ARGD, arginase deficiency; ASD, argininosuccinic acid synthetase deficiency or "citrullinemia"; CITRD, citrin transporter defect; CPSID, carbamoyl phosphate synthetase I deficiency; ORNT1, ornithine transporter; OTCD, ornithine transcarbamylase deficiency.

vaccination counted as day 0) was compared with HAE incidence outside the postvaccination periods. Vaccine history for each child was ascertained from the child's medical record by trained study coordinators; in the case of incomplete records, additional vaccination data came from parents and primary care physicians. Vaccinations administered included diphtheria-tetanus-acellular pertussis vaccine; hepatitis A vaccine; hepatitis B (HepB) vaccine, alone or with the diphtheria-tetanus-acellular pertussis vaccine;

Haemophilus influenzae type b; trivalent inactivated influenza vaccine; inactivated poliovirus vaccine; oral polio vaccine; measles-mumps-rubella vaccines; 7-valent pneumococcal conjugate vaccine; live attenuated rotavirus vaccine; and live attenuated varicella vaccine. When children experienced an HAE, study coordinators completed interim event forms designed specifically to capture recent vaccine exposures. Laboratory analysis of plasma ammonia levels and specific amino acids (glutamine, glycine, alanine, argi-

nine, and citrulline) were routinely performed when an HAE occurred. Demographic and clinical features were included in the UCD database, including specific urea cycle diagnoses and suspected HAE triggers.

Data Analysis

We conducted analyses using the self-controlled case series (SCCS) method and conditional Poisson regression to calculate relative incidence ratios of HAEs in the postvaccine-exposure versus nonexposure periods while controlling for patient age in 1-year increments.^{16,17} Our underlying hypothesis was that HAE rates were not temporally associated with acute exposure to vaccination, after correction for age; the null hypothesis was that HAE events would not depart significantly from a Poisson distribution over time. In accordance with the SCCS design, analysis was restricted to patients with at least 1 documented vaccination and at least 1 HAE. Rate ratio was defined as HAE rate in a given postvaccination exposure period versus HAE rate in the observation time occurring outside of that period. Given that a child may be metabolically unstable and at risk for HAE recurrence in the days immediately after an acute HAE, clustering of HAEs was defined as 2 HAEs co-occurring within 21 days of each other. A sensitivity analysis was performed of the Poisson count model (comparing HAE cluster frequency in 21-day postvaccination windows with frequency at all other times by z test for 2 proportions) to determine its robustness to the departure of HAE from the assumption of independent events. The Mann-Whitney test was used to compare age, and Pearson's χ^2 test was used to compare demographic characteristics and vaccine subtypes. Adjustment for multiple comparisons in the secondary analysis of the distribution of multiple vaccine subtypes was performed using standard Bon-

TABLE 2 Vaccinations Within 7- or 21-Day Window of HAE

Vaccine	All Ages			≥30 d of Age		
	<i>n</i> (%)	Vaccine ≤7 d of HAE, <i>n</i> (%)	Vaccine ≤21 d of HAE, <i>n</i> (%)	<i>n</i> (%)	Vaccine ≤7 d of HAE, <i>n</i> (%)	Vaccine ≤21 d of HAE, <i>n</i> (%)
DTaP	244 (22.2)	2 (9.5)	7 (17.1)	242 (23.3)	2 (20.0)	7 (25.0)
DTaP-HepB-IPV	45 (4.1)	3 (14.3)	6 (14.6)	45 (4.3)	3 (30.0)	6 (21.0)
DTaP-Hib	40 (3.6)	0 (0.0)	0 (0.0)	40 (3.8)	0 (0.0)	0 (0.0)
Hepatitis A	45 (4.1)	0 (0.0)	1 (2.4)	45 (4.3)	0 (0.0)	1 (3.6)
HepB	164 (14.9)	10 (47.6)	13 (31.7)	115 (11.1)	0 (0.0)	2 (7.1)
Hib	49 (4.5)	0 (0.0)	1 (2.4)	49 (4.7)	0 (0.0)	1 (3.6)
Influenza	152 (13.9)	3 (14.3)	5 (12.2)	152 (14.6)	3 (30.0)	5 (17.0)
IPV	53 (4.8)	0 (0.0)	3 (7.3)	52 (5.0)	0 (0.0)	3 (11.0)
MMR	65 (5.9)	1 (4.8)	2 (4.9)	64 (6.2)	1 (10.0)	2 (7.1)
Other	240 (22.0)	2 (9.5)	3 (7.3)	235 (22.6)	1 (10.0)	1 (3.6)
Total	1097 (100.0)	21 (100.0)	41 (100.0) ^a	1039 (100.0)	10 (100.0)	28 (100.0)

DTaP indicates diphtheria-tetanus-acellular pertussis vaccine; IPV, inactivated poliovirus vaccine; Hib, *Haemophilus influenza* type b; MMR, measles-mumps-rubella.

^a Forty-two HAEs; 3 patients had 2 HAEs within 21 days from the same vaccine, 2 patients had an HAE within 21 days of 2 vaccines taken, and both vaccines were counted.

ferroni correction methods; the primary analysis was not corrected because the Bonferroni method is overly conservative in the context of a main outcome involving vaccine safety.¹⁸ Conditional Poisson regressions were conducted by using Stata 10 (Stata Corp, College Station, TX), and the remainder of analyses were performed with R 2.9 (R Development Core Team, Vienna, Austria) by using supplemental packages Hmisc, Design, chron, and gnm.

In addition to analysis of all types of vaccine exposures, a separate analysis was also performed for exposure to influenza vaccine alone; vaccines are frequently administered in batches, each of which is counted as an individual exposure (Table 2 lists the multiple exposures that occurred). Sample size calculations for the present study were not performed before the formation of the UCD Consortium (UCDC). However, we estimated power posthoc for the SCCS methods using the procedures of Musonda et al,¹⁹ allowing for decreasing age effects. Thus, in the context of this study, the risk of HAEs was taken to be greatest in the newborn period, lesser in infancy, and further decreased in older children.

Human Subject Protection

All participating members of the National Institutes of Health–approved Rare Diseases Clinical Research Consortium for UCD also obtained local institutional review board approval, and the study was endorsed by the National Urea Cycle Disorders Foundation.

RESULTS

A total of 169 patients with UCDs were enrolled in the National Institutes of Health–Rare Diseases Clinical Research Consortium for UCD, and vaccination records were obtained for 112 patients. Of these, 74 experienced at least 1 HAE. The characteristics of patients with and without HAEs after vaccination are given in Table 1. There were no statistically significant differences between patients with and without vaccination records in the types of UCDs, onset of hyperammonemia in first 30 days of life, or hospital where care was provided. Factors associated with unobtainable vaccination records included older mean age of patient at enrollment (11 vs 7 years; $P = .001$) and the occurrence of HAEs during the study period ($P < .001$).

The median age of all children ($N = 169$) enrolled in the UCDC was 9 years

TABLE 3 Frequency Distribution of HAEs According to Patient Age

Age, y	No. of HAEs	Percentage of Total HAEs	Cumulative HAE Counts	Cumulative Frequency, %
0	117	32	117	32
1	37	10	154	42
2	38	10	192	52
3	29	8	221	60
4	29	8	250	67
5	15	4	265	71
6	21	6	286	77
7	15	4	301	81
8	25	7	326	88
9	17	5	343	92
10	5	1	348	94
11	3	1	351	95
12	2	1	353	95
13	9	2	362	98
14	4	1	366	99
15	1	0	367	99
16	2	1	369	99
17	2	1	371	100
Total	371	100	371	100

(interquartile range: 4–13) (Table 1). Risk of HAE decreased with age, as anticipated. The frequency distribution of HAE by year of age is given in Table 3. More than three-quarters of all HAEs occurred by 6 years old, the age at which children should typically be fully immunized against all vaccine-preventable early childhood diseases. The mean number of vaccines administered was 9.8 (SD: 4.7) among all 112 children with UCD, and 9.7 (SD: 4.9) among the 74 patients with ≥1 HAE. There were 1097 vaccination events and 371 HAEs, in total. The mean age for all 112 children was 7.5 years, and 7.0% of the total observation time for all patients was classified as being within the 21-day exposure windows after any vaccination. Thus, 93% of the time, children were not at risk for hypothetical triggering of an HAE by a vaccine; this was the unexposed person-time period.

In an effort to investigate the possibility that a particular type of vaccination might be overrepresented in the list of vaccines given in the immediate 7- or 21-day periods preceding an HAE, we examined the relative frequency of vaccine types preceding HAEs com-

TABLE 4 Relative Incidences for HAEs in Relation to Vaccine Exposure

	Risk Period: Days After Vaccination	RI (95% CI)	RI (95% CI), Adjusted for Age
All ages, all vaccines			
74 patients	1–7	1.92 (1.19–3.10)	1.31 (0.80–2.13)
74 patients	8–21	1.32 (0.87–2.01)	0.91 (0.59–1.39)
74 patients	1–21	1.53 (1.10–2.11)	1.05 (0.74–1.47)
≥30 d of age			
74 patients	1–7	1.05 (0.54–2.03)	0.72 (0.37–1.41)
74 patients	8–21	1.23 (0.79–1.93)	0.86 (0.54–1.35)
74 patients	1–21	1.17 (0.80–1.71)	0.81 (0.55–1.20)
Influenza only			
31 patients	1–7	2.20 (0.70–3.93)	2.31 (0.73–7.30)
31 patients	8–21	0.73 (0.18–2.97)	0.78 (0.19–3.12)
31 patients	1–21	1.22 (0.50–3.00)	1.28 (0.52–3.15)

RI indicates relative incidence; CI, confidence interval.

pared with the overall frequency of vaccinations given in the 74 patients with ≥ 1 HAE (Table 2). Of all vaccine exposures occurring up to 21 days before HAE, only HepB vaccine and diphtheria-tetanus-acellular pertussis–HepB–inactivated poliovirus vaccine were more frequent than expected by chance alone using Fisher’s exact test (31.7% and 14.6%, respectively). However, with categorical adjustment for age, no vaccine frequency was significantly greater than expected, after correcting for multiple comparisons.

We constructed an age-adjusted Poisson regression model to test the temporal relationship between HAEs and vaccine exposure. Of the 112 patients with at least 1 recorded vaccine exposure, 74 also had at least 1 HAE diagnosed at any time and were included in the Poisson regression analysis, as per the requirement of the SCCS method that each informative individual must have had exposure as well as event occurrence. The results are reported in Table 4. As expected, a statistically significant elevation of the crude relative incidence of HAE occurred in newborns during the 7- and 21-day windows after the HepB vaccination shortly after birth, when neonatal catabolism and first exposure to milk protein promote HAE regardless of vaccine exposure. With Poisson model adjustment for age, however,

there was no statistically significant difference in the relative incidence of HAEs. Age adjustment was most pertinent in the neonatal period, given that crude HAE incidence rates were not elevated after 30 days of life (Table 4). Of the 74 patients, 42 had HAEs at <30 days of age, and of these, 15 received the HepB vaccine at birth, yet the HAE occurred at a mean age of 10.7 days with a wide SD (10.4) and no predictable time course after vaccination exposure. A separate analysis of influenza vaccine exposure alone in 31 patients (of the 74 patients who had vaccine exposure and an HAE) also showed no increase in risk of HAE (Table 4).

We performed a sensitivity analysis for HAE clustering and found no association with vaccine-exposure status. We identified 70 HAEs that occurred within 21 days of each other. Of these HAEs, 7 also fell within a 21-day postvaccination period. However, the relative incidence of such HAE clusters was highly similar and not significantly different in the postvaccination period than at any other time (difference in proportions: 0.0001; $z = 0.97$; $P = .33$).

DISCUSSION

We found no evidence to support the hypothesis that childhood vaccine-exposure triggers HAEs in children with UCDs. Given their vulnerability to

catabolic decompensation and HAEs in the setting of fever or acute inflammatory or infectious response, it is particularly important to avoid vaccine-preventable diseases in patients with UCDs. Thus, we conclude that the known preventive benefits of immunization likely outweigh any residual theoretical risk of triggering HAEs in these patients.

The UCD registry is an unprecedented resource for the study of the safety of vaccines in vulnerable patient populations, and our study is, to our knowledge, the largest controlled comparison published on this topic. Given the challenges of assembling sufficient sample sizes of patients with rare diseases, the UCD registry represents a successful model that may potentially be extended to the study of vaccine safety in other groups of patients with IEM. The current practice of assessing vaccine safety within the voluntary Vaccine Adverse Event Reporting System is informative but only if IEM are cited as potential predisposing factors on reporting forms. To compare our findings with information in this voluntary reporting system, we researched the past 5 years of their database and found no citations of UCDs in relation to adverse events after vaccines. Likewise, we are unaware of any deaths in patients with UCD occurring in the 2009–2010 H1N1 flu pandemic, although there is no systematic method for reporting such occurrences in patients with UCDs. The extent to which H1N1 immunization was effective at preventing HAEs is unknown, and should be a topic for future research.

This was a cross-sectional study, and capture was estimated at 27% of all eligible patients, the highest recruitment rate for any disorder in the Rare Diseases Clinical Research Consortium.⁸ Although the general limitations of nonrandom sampling apply to the present study, recruitment was unre-

lated to the question of vaccination as a possible trigger for HAE, and we do not perceive a substantial potential for bias. One additional limitation of our study design was that immunization data were not prospectively collected and some vaccination records were obtained from primary care providers, if tertiary care hospital records were lacking. Patients with UCDs are highly reliant on metabolic specialty centers; in the experience of the UCDC, it is rare for any patient to be lost to follow-up. Therefore, our clinical ascertainment of HAE is considered to be essentially complete, although it was not possible to document complete vaccination exposures on all patients. We considered the possibility that missing vaccine data could potentially represent a systematic bias against the hypothesis that HAEs could be triggered by vaccines. However, the UCDC was focused on clinical management of UCDs, and when children experienced an HAE, recent vaccine exposure was specifically elicited by study coordinators. Therefore, we would anticipate that any resulting vaccine-exposure ascertainment bias would likely favor temporal correlation of recent vaccines with HAEs, which we did not observe.

For the primary statistical analysis, we relied on the SCCS method, which is considered to be the optimal method for relating recurrent time-dependent events.^{16,17} The SCCS method assumes variability in the timing of events and exposures. In the neonatal period, this assumption is almost uniformly violated, in that newborns with UCDs receive first exposure to milk protein at essentially the same time as their first HepB vaccine exposure. Therefore, vaccines administered in the immediate neonatal period are essentially uninterpretable by the SCCS method. Although a temporal association between HepB vaccination and HAE is possible, age-adjustment of the Pois-

son model adequately corrected for the known age effect, and importantly, restricting the analysis to >30 days of age found no significant association even without further age adjustment. In addition, on the basis of our sensitivity analysis of the Poisson count model to HAE clustering, we found that such clustering did not bias our results. We also considered the possibility that physicians may have been less likely to administer scheduled vaccinations to metabolically unstable children who had recently experienced an acute HAE. We acknowledge that our study was not designed to assess the safety of vaccination of recently ill, metabolically unstable children, and advocate that physicians consider waiting ~21 days before administering vaccines unless the risks of vaccine deferral seem to outweigh theoretical concerns about triggering an HAE recurrence.

Our study is the largest that we know of to have investigated an association between vaccination and HAE, and our posthoc estimates indicated 80% power to detect risks less than twofold. Indeed, the expected elevation in relative incidence of HAEs stemming from the diagnosis in the newborn period coinciding with the time of HepB vaccination was readily detected in our study, demonstrating adequate power for risks of 1.5 and 1.9 (Table 4). Such apparent risk increases were statistically significant before age adjustment, although the newborn period represents only a small fraction of total observation time, HAE, and vaccine exposures. In addition, given 371 HAEs and 7% of observation time spent within 21-day postvaccination windows, we estimated that our study had 80% power to detect a 1.8-fold risk increase for HAEs caused by vaccination exposure, even when conservatively incorporating into our model a decreasing age effect (ie, decline in

nonvaccine-associated risk of hyperammonemia) from birth to older ages) that is known to reduce power substantially. Therefore, we do not consider a type II (false-negative) error to be a likely explanation for our overall null findings. Theoretical small risks of vaccinations not detectable in this study must be weighed against the known benefits of childhood immunizations.

CONCLUSIONS

We have presented evidence that childhood immunizations do not seem to trigger HAEs in children with UCDs. Because it is typically not possible to know that a child is developing hyperammonemia in the newborn period before the HepB vaccine is administered, we do not recommend any modification in HepB vaccine administration at birth. Our overall recommendation, based on our data, is that if children are clinically well, have no standard contraindications, and are in acceptable metabolic control, all vaccinations, including influenza, should be given according to the recommended schedule. The apparent lack of vaccine-triggered complications in this medically fragile population provides reassurance in the context of broader societal concerns about vaccine safety in potentially vulnerable children. Additional research should focus on vaccine safety in a wide variety of IEM including mitochondrial disease, organic acidurias, and fatty acid oxidation disorders.

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University of California at Los Angeles (UCLA), Los Angeles, CA; University Children's Hospital, Zurich, Switzerland; Yale University School of Medicine, New Haven, CT; and Vanderbilt University Medical Center, Nashville, TN.

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