DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

August 17, 2018

SENT VIA EMAIL

Aaron Siri
Sire and Glimstad, LLP
200 Park Avenue
Seventeenth Floor
New York, New York 10166
aaron@sirillp.com

Dear Mr. Siri:

This letter is regarding to your Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Freedom of Information Act (FOIA) request of May 31, 2018, assigned #18-00770-FOIA, seeking,

> "Any email communications sent to or received by Frank DeStefano during January 2018 which contain any of the following words or phrases: "Autism", "ASD", or "Neurodevelopmental Disorder."

We located 51 pages of responsive records. After a careful review of these pages, some information was withheld from release pursuant to 5 U.S.C. §552 Exemptions 5 and 6.

Exemption 5 protects inter-agency or intra-agency memorandums or letters which would not be available by law to a party other than an agency in litigation with the agency. Exemption 5 therefore incorporates the privileges that protect materials from discovery in litigation, including the deliberative process, attorney work-product, and attorney-client privileges. Information withheld under this exemption was protected under the deliberative process privilege. The deliberative process privilege protects the decision-making process of government agencies. The deliberative process privilege protects materials that are both predecisional and deliberative. The materials that have been withheld under the deliberative process privilege of Exemption 5 are both predecisional and deliberative, and do not contain or represent formal or informal agency policies or decisions. Examples of information withheld include draft responses.

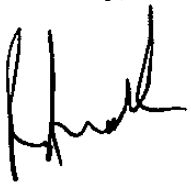
Exemption 6 protects information in personnel and medical files and similar files when disclosure would constitute a clearly unwarranted invasion of personal privacy. The information that has been withheld under Exemption 6 consists of personal information, such as names, phone numbers, home addresses, email addresses, and we have determined that the individual/s to whom this information pertains have a substantial privacy interest in withholding it.

In accordance with the Department's implementing regulations, 45 CFR Part 5, no fees were assessed for processing your request #18-00770-FOIA.

You may contact our FOIA Public Liaison at 770-488-6277 for any further assistance and to discuss any aspect of your request. Additionally, you may contact the Office of Government Information Services (OGIS) at the National Archives and Records Administration to inquire about the FOIA mediation services they offer. The contact information for OGIS is as follows: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road-OGIS, College Park, Maryland 20740-6001, e-mail at ogis@nara.gov; telephone at 202-741-5770; toll free at 1-877-684-6448; or facsimile at 202-741-5769.

If you are not satisfied with the response to this request, you may administratively appeal by writing to the Deputy Agency Chief FOIA Officer, Office of the Assistant Secretary for Public Affairs, U.S. Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Avenue, Suite 729H, Washington, D.C. 20201. Please mark both your appeal letter and envelope "FOIA Appeal." Your appeal must be postmarked or electronically transmitted by Thursday, November 15, 2018.

Sincerely,



Roger Andoh
CDC/ATSDR FOIA Officer
Office of the Chief Operating Officer
(770) 488-6399
Fax: (404) 235-1852

Enclosures

18-00770-FOIA

From: (b)(6)
Sent: 24 Jan 2018 17:33:10 +0000
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: Does vaccinating infants cause Autism? FactCheck Invitation..

Dear Dr DeStefano,

Given your expertise, we would really appreciate if you could answer this question that has been asked from a member of the public: "Does vaccinating infants cause Autism?".

This is part of our recently launched FactCheck initiative to better share evidence from verified researchers to allow journalists and the wider public to learn & share the facts widely. Only experts like you can answer and you can contribute as much or as little as you feel necessary - however the more PhDs/experts who can answer gives much wider benefit/power to the public.

Please click here to answer & help us bring evidence back into public discourse.

Many thanks Dr DeStefano!

Warmest regards,

(b)(6)

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 24 Jan 2018 18:57:14 +0000
To: Vaughn, William (CDC/OID/NCEZID) (CTR)
Cc: Miller, Kenneth (CDC/OCOO/OCIO/ITSO) (CTR)
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Not sure if I need to answer this or if we can provide a standard response.
Frank DeStefano, MD, MPH
From: (b)(6)
Sent: Wednesday, January 24, 2018 12:33 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: Does vaccinating infants cause Autism? FactCheck Invitation..
Dear Dr DeStefano,

Given your expertise, we would really appreciate if you could answer this question that has been asked from a member of the public: "Does vaccinating infants cause Autism?".

This is part of our recently launched FactCheck initiative to better share evidence from verified researchers to allow journalists and the wider public to learn & share the facts widely. Only experts like you can answer and you can contribute as much or as little as you feel necessary - however the more PhDs/experts who can answer gives much wider benefit/power to the public.

Please click here to answer & help us bring evidence back into public discourse.

Many thanks Dr DeStefano!

Warmest regards,
(b)(6)

From: Cano, Maria (CDC/OID/NCEZID)
Sent: 24 Jan 2018 15:47:36 -0500
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

FYI

From: Cano, Maria (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 3:03 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

We can only provide the information that we already have on autism in the CDC website.
As Frank noted below, he does not need to answer the question directly or provide a specific response.

From: Miller, Elaine R. (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 2:52 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Cano, Maria (CDC/OID/NCEZID) <zqg9@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Hi William,
I am forwarding this to Beth. She is covering inquiry response since I am not in the office today.
Thanks,
Elaine

From: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Date: January 24, 2018 at 2:09:26 PM EST
To: Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>, Sharan, Martha (CDC/OID/NCEZID) (CTR) <liu4@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Hey there – Elaine, I think Frank accidentally forwarded this to the wrong "miller." This is a bit unusual in that it's an invitation to comment on this guy's website (b)(6). Is there a precedent for this kind of thing? I don't think it's a "real" inquiry…it's more like "we're building "expert" content for our website/platform…and want you to chime in on a hot topic"

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 1:57 PM
To: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Miller, Kenneth (CDC/OCOO/OCIO/ITSO) (CTR) <wut4@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Not sure if I need to answer this or if we can provide a standard response.

Frank DeStefano, MD, MPH

From: (b)(6)
Sent: Wednesday, January 24, 2018 12:33 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: Does vaccinating infants cause Autism? FactCheck Invitation..

Dear Dr DeStefano,

Given your expertise, we would really appreciate if you could answer this question that has been asked from a member of the public: "Does vaccinating infants cause Autism?".

This is part of our recently launched FactCheck initiative to better share evidence from verified researchers to allow journalists and the wider public to learn & share the facts widely. Only experts like you can answer and you can contribute as much or as little as you feel necessary - however the more PhDs/experts who can answer gives much wider benefit/power to the public.

Please click here to answer & help us bring evidence back into public discourse.

Many thanks Dr DeStefano!

Warmest regards,

(b)(6)

From: (b)(6)
Sent: 19 Jan 2018 11:33:54 -0500
To: (b)(6);Destefano, Frank (CDC/OID/NCEZID);(b)(6)
Subject: FW: Four article reprints
Attachments: Blood & Hair Aluminum Levels article.pdf, On-Time Vaccine Receipt article.pdf, Increasing exposure to antibody article.pdf, Aluminium adjuvanted vaccines article.pdf

Another set of documents for the call, not necessary to read, sent as examples

From: (b)(6)
Sent: Friday, January 19, 2018 9:04 AM
To: (b)(6)
Subject: Four article reprints

(b)(6)

Blood and Hair Aluminum Levels, Vaccine History, and Early Infant Development: A Cross-Sectional Study

Mateusz P. Karwowski, MD, MPH; Catherine Stamoulis, PhD; Larissa M. Wenren, BA; G. Mayowa Faboyede, MS; Nicolle Quinn, MS, RD, LDN; Kathleen M. Gura, PharmD; David C. Bellinger, PhD, MSC; Alan D. Woolf, MD, MPH

From the Pediatric Environmental Health Center (Drs Karwowski and Woolf), Boston Children's Primary Care at Longwood (Ms Wenren), Division of General Pediatrics, Boston Children's Hospital; Division of Adolescent Medicine (Dr Stamoulis, Ms Faboyede, and Ms Quinn), Department of Neurology (Drs Stamoulis, and Bellinger), Department of Pharmacy (Dr Gura), Boston Children's Hospital, Region 1 New England Pediatric Environmental Health Specialty Unit (Drs Karwowski and Woolf), and Harvard Medical School (Drs Karwowski, Stamoulis, and Woolf), Boston, Mass

The authors have no conflicts of interest to disclose.

Address correspondence to Alan D. Woolf, MD, MPH, Pediatric Environmental Health Center, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (e-mail: alan.woolf@childrens.harvard.edu).

Received for publication May 24, 2017; accepted September 3, 2017.

Abstract

Objective: To evaluate relationships between whole blood (B-Al) and hair aluminum (H-Al) levels in healthy infants and their immunization history and development.

Methods: We conducted a cross-sectional study of 9- to 13-month-old children recruited from an urban primary care center, excluding those with a history of renal disease or receipt of either aluminum-containing pharmaceuticals or parenteral nutrition. Aluminum levels were measured using inductively coupled plasma-mass spectrometry. Correlation with Bayley Scales of Infant and Toddler Development, Third Edition (BSID) and vaccine-related aluminum load was assessed via linear regression models.

Results: The median age of 85 participants was 287 days. B-Al (median, 15.4 ng/mL; range, 0.9–952 ng/mL) and H-Al (median 42,542 ng/g; range, 2758–211,690 ng/g) were weakly correlated (Spearman $\rho = 0.26$; $P = .03$). There was no significant correlation between B-Al or H-Al and estimated aluminum load from vaccines. B-Al was not correlated with BSID composite or subscale scores. Although H-Al was not correlated with BSID scores in models including all data ($n = 85$), it was inversely correlated with motor composite ($P < .02$; Wald $= 5.88$) and the gross motor subscale ($P = .04$; Wald $= 4.38$) in models that excluded an extreme outlying H-Al value.

Conclusions: Infant B-Al and H-Al varied considerably but did not correlate with their immunization history. Likewise, there was no correlation between B-Al and infant development or between H-Al and language or cognitive development. An inverse correlation between H-Al and BSID motor scores deserves further investigation.

Keywords: aluminum biomarkers; aluminum toxicity; immunizations; metals toxicity; neurodevelopment; vaccines

Academic Pediatrics 2017;■:1–5

What's New

Concerns have been raised about aluminum-containing vaccines. In this exploratory study we found no correlation between infant blood or hair aluminum concentrations and vaccine history or between blood aluminum and developmental status. Correlations between hair aluminum and motor development were observed.

ALUMINUM IS FOUND in many consumer goods: cookware, packaging, medicines and foodstuffs, including vaccines and infant formulas.[1–5] Although exposure is common, only a small percentage of ingested aluminum is absorbed; it has no known physiologic role.[6] Nevertheless, adverse health effects have been documented in children and adults exposed via exogenous introduction (eg, pharmaceuticals, dialysate, parenteral nutrition) who have excessive absorption or impaired excretion (eg, decreased glomerular filtration in infancy or as a result of renal impairment), or both.[4,6–8] Neurologic consequences of chronic aluminum toxicity include behavior changes, reduced intelligence, and encephalopathy.[4–7]

Although aluminum toxicity has been described in populations at high risk for exposure or retention, few studies have examined health effects of incidental aluminum exposure in healthy infants. Because of immaturity of their gastrointestinal wall, renal system, and blood–brain barrier, infants might be more vulnerable than older children to aluminum exposure.[1] The safety of aluminum adjuvants used to increase the effectiveness of childhood immunizations routinely given during infancy has been well established[9] but recently called into question.[10–12] In this exploratory study we aimed to determine whether blood (B-Al) and hair aluminum (H-Al) concentrations in

healthy infants correlated with their immunization history and measures of their neurodevelopment.

METHODS

Study Design

We obtained data for this cross-sectional study from a cohort of healthy infants presenting to an urban, primary care center for well child care. We obtained written informed consent from the study participants' legal guardians in either English or Spanish; the study was approved by the hospital's institutional review board.

Power

Sample size calculations were on the basis of the goal to derive a reference range for B-Al in infants. Assuming aluminum, like other trace metals, follows a log-normal distribution, we estimated that a sample size of $n = 65$ would provide the desired level of precision (± 1 on the logarithmic scale) for characterizing the distribution of B-Al. To account for nonretention, missing data, and unforeseen circumstances, target recruitment was increased to 80 infants.

Study Population

We recruited 9- to 13-month-old infants from English- or Spanish-speaking families who were scheduled for well child visits. Families learned about the study through one of various outreach strategies: flyers, letters, phone calls, or from study staff in the clinic. We excluded infants with a history of chronic renal failure or receipt of either aluminum-containing antacids or total parenteral nutrition because their tissue aluminum stores might be unusually high.[4–7,13] We excluded infants born before 37 weeks' gestation or weighing <2500 g at birth. Of 504 families receiving recruitment letters, 92 agreed to participate; 7 infants were excluded because of ineligibility or incomplete data collection. We analyzed data for 85 infants who met inclusion criteria and for whom information was obtained on aluminum levels as well as on neurodevelopment. Medical records of contemporaneous infants of a comparable age and sex were randomly selected from families who could not be reached and compared with study participants for race, ethnicity, and medical insurance type to evaluate the potential for selection bias.

Data Collection and Management

We collected information on demographic characteristics, birth, medical histories, medications, and immunization status from medical records, confirming it with caregivers via standardized interview. Vaccine-related aluminum load for each subject was calculated using immunization histories redacted from medical records, published data on vaccine aluminum content, and assumptions of 100% bioavailability. We managed data using the Research Electronic Data Capture database system.[14]

Laboratory Measures

Because aluminum could easily contaminate specimens, we took considerable measures to preserve sample integrity. Parents were instructed to avoid using shampoo on their infant's hair before the study visit. Equipment used for blood and hair collection came from sealed batches prescreened for aluminum contamination. Negligible background contribution of aluminum from blood collection supplies was confirmed by analyzing deionized water sent through the whole blood collection system.

Hair was collected and placed in paper envelopes. Blood samples were collected in aluminum-free plastic cryotubes and stored at $-80^{\circ}C$ until analysis at the Harvard School of Public Health Trace Metals Laboratory. All steps in the preparation of samples and reagents were performed in a class 1000 clean room; sample digestion was carried out in a class 100 clean hood. All reagents were certified as containing <5 to 10 parts per trillion aluminum.

Hair samples were sonicated in 10 mL 1% (vol/vol) aluminum-free certified Triton X-100 Omnipur (Millipore Sigma, Billerica, Mass) solution for 5 minutes followed by rinsing 5 times with distilled, deionized, aluminum-free water and then placed in a drying oven at $60^{\circ}C$ for 24 hours. Hair samples were weighed into a metals-free 15-mL polyethylene BD Falcon tube (BD Biosciences, Franklin Lakes, NJ) and 1 mL of UltraPure Nitric Acid (VWR Chemicals, Radnor, Pa) was added. The sample was digested overnight and diluted to 5 mL for analysis.

Blood was weighed into a 15-mL metals-free polyethylene BD Falcon tube (BD Biosciences) and digested with 1 mL UltraPure Nitric Acid overnight, followed by addition of 0.5 mL of UltraPure Hydrogen Peroxide (VWR Chemicals). Samples were then diluted to 5 mL for analysis.

Acid-digested samples were analyzed in 5 replicates using inductively coupled plasma-mass spectrometry (Perkin Elmer Elan DRC-II ICP-MS, Norwalk, Conn); the average value was reported. Quantification was free of analytical interference; mean recovery rates were 90% to 110%. Accuracy was checked using continuous calibration verification standards run after every 10 samples and at the end of the analysis.

Because aluminum was mono-isotopic, inductively coupled plasma-mass spectrometry measurement was performed at M/Z 27. The isotope used was free of spectral interference for this matrix type; no correction was required. Replicate measurements had good reproducibility. Analytic limits of detection for aluminum were 100 ng/g (hair) and 0.1 ng/mL (blood). Using these parameters and detection limits, reliable measurements were obtained from as little as 1.65 mg of hair sample and 0.1 mL of blood sample.

We obtained additional measures during the visit and from the medical record: serum creatinine and blood urea nitrogen as proxy measures of infant renal function; blood counts, ferritin, and reticulocyte hemoglobin concentrations as measures of iron sufficiency; and venous blood lead levels.

Developmental Testing

Motor, language, and cognitive development were measured using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID).[15] The BSID yields composite scores for cognitive, language, and motor domains. Language is divided into receptive and expressive

communication scaled scores; motor into fine and gross motor scaled scores. Caregivers also completed the Social-Emotional and Adaptive Behavior Questionnaires, yielding social-emotional and general adaptive composite scores. All composite scores were age-adjusted, with a mean of 100 and SD of 15.

We reported summary statistics for variables with normal (mean, SD) and non-normal (median and interquartile range [IQR]) distributions. We compared demographic data using parametric (z-score) or nonparametric (Wilcoxon rank sum) tests, when appropriate. We reported the correlation between B-Al and H-Al values using Spearman rank correlation (ρ). We assumed a statistical significance level of 0.05.

We used linear regression models to assess the correlation between individual or combined BSID scores and B-Al or H-Al concentrations, and to evaluate the effects of potential confounders including age, race, gender, maternal and paternal age, maternal education, family income, estimated cumulative vaccine aluminum load, and venous blood lead level. The correlation between B-Al and H-Al levels and estimated cumulative vaccine aluminum load was assessed. We calculated the IQRs, a measure of statistical dispersion. We used well established definitions for moderate and extreme outliers median $\pm$ 1.5 $\times$ IQR and median $\pm$ 3 $\times$ IQR, respectively[16] to estimate outlying blood and aluminum values. We assessed the relationship between aluminum biomarkers and BSID scores after excluding extreme outliers. Analyses were performed using the software MATLAB, release 2014a (Mathworks Inc, Natick, Mass).

RESULTS

Table 1 shows the demographic characteristics of 85 study participants (median age, 287 days) and their families. There were no significant differences between participants and 85 eligible but nonparticipating infants according to race, ethnicity, or medical insurance type. Study participants were born after an average 39-week gestation and had normal renal function; none had evidence of anemia or a blood lead value exceeding the reference (5 μg/dL).[17] No infant scored $\geq$2 SDs below the mean on any subscale of the BSID.

Three participants were missing H-Al data and 5 were missing B-Al data. Median H-Al (42,542 ng/g); 95% confidence interval (CI), 32,527–52,957 ng/g; IQR = 51,408 ng/g) was several orders of magnitude greater than median B-Al (15.4 ng/mL; 95% CI, 12.7–19.5; IQR = 19.3 ng/mL). When the single extreme outlying H-Al value (211,690 ng/g) was excluded, median H-Al was 42,485 ng/g; 95% CI, 32,524–52,655 ng/g; IQR = 47,830 ng/g). When the 7 extreme outlying B-Al values (in the range 98-952 ng/mL) were excluded, median B-Al was 14.3 ng/mL (95% CI, 11.6–18.2; IQR = 13.9 ng/mL). Neither H-Al nor B-Al levels was correlated with age ($P > .4$). There was a weakly positive correlation between H-Al and B-Al (Spearman $\rho = 0.26$; $P = .03$), as shown in the Figure. Infants missing either H-Al or B-Al values and those with extreme outlying values (a total of 14 samples) were excluded from the scatter plot.

Table 1. Characteristics of Study Participants and Families

Characteristic	Study Participants (N = 85)
Mean/median age (25th–75th percentiles), days	
Male	299/286 (277–301)
Female	300/289 (277–305)
Female sex	41 (48%)
Age, years*	
Mother	30.0 ± 6.3
Father	32.1 ± 6.7
Predominant language spoken at home	
English	59 (69)
Spanish	8 (9)
Other	16 (20)
Not available	2 (2)
Race	
Black	37 (44)
White	4 (5)
Other	32 (38)
Not available	12 (14)
Ethnicity	
Hispanic	19 (22)
Non-Hispanic	58 (68)
Not available	8 (9)
Insurance	
Public	68 (80)
Private	15 (18)
Not available	2 (2)
Maternal education level	
Less than high school	4 (5)
Some high school	9 (11)
Completed high school	14 (16)
Some college	25 (29)
Completed college	27 (32)
Other	4 (5)
Not available	2 (2)
Annual family income	
<$20,000	36 (42)
$20,000 to $49,999	23 (27)
≥$50,000	11 (13)
Not available	15 (18)

Data are presented as mean ± SD or n (%) except where otherwise stated.

*Age data missing for 2 mothers and 4 fathers.

Table 2 contains P values and Wald statistics for statistically significant regression coefficients for B-Al and H-Al from models that assessed their correlation with BSID scores (scores were not compared with each other but were assessed independently). Age, sex, race/ethnicity, family income, and blood lead level were not significant covariates in these regression models. Median estimated cumulative vaccine aluminum load was 2.9 mg (range, 1.43–3.55 mg; IQR = 0.11 mg). There was no statistically significant correlation between B-Al or H-Al and estimated cumulative aluminum load from vaccines (Spearman $\rho = -0.13$, $P = .26$ for B-Al; $\rho = 0.06$, $P = .56$ for H-Al).

B-Al levels were not correlated with BSID scores. When the single extreme outlying H-Al value was

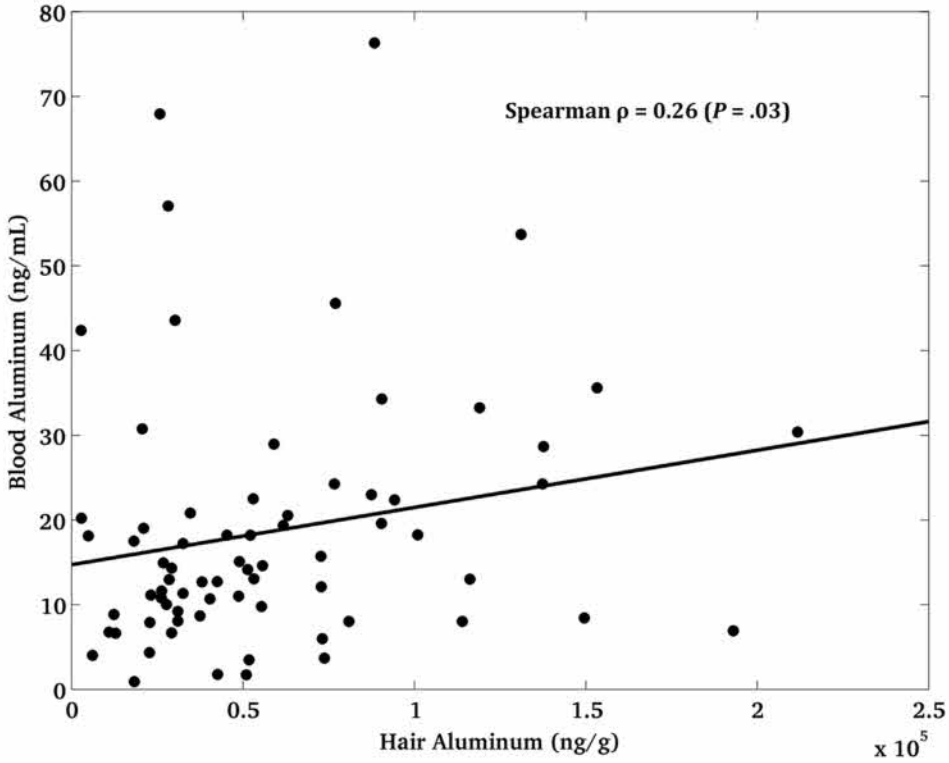


Figure. *Scatter plot of hair aluminum versus blood aluminum levels (n = 71). Participants missing either hair or blood aluminum data, as well as 7 extreme blood aluminum outliers and 1 extreme hair aluminum outlier, were excluded (ie, a total of 14 samples).*

excluded from the model, there was a significant positive correlation between H-Al and the motor composite score ($P = .02$; Wald = 5.88) as well as the gross motor score ($P = .04$; Wald = 4.38), but not the fine motor score ($P = .11$). The infant with the extreme outlying H-Al value also had composite and gross motor scores <25th percentile. Excluding the 7 outlying B-Al values from the models did not change the (lack of) significance of the correlations between B-Al and BSID scores (see Table 2). Sensitivity analyses using log-transformed aluminum values did not yield different results.

DISCUSSION

Whole B-Al levels in these infants were higher than previously reported serum and plasma aluminum reference levels, which might reflect differences in the populations or longer retention time of aluminum in red blood cells.[18,19] Median H-Al levels among our cohort (42,542 ng/g) were comparable with previously reported levels in 37 children aged 26 to 825 days (47,700 ng/g).[20] There was a statistically significant, weak correlation between whole B-Al and H-Al.

Table 2. *P* Values and Select Wald Statistics (Shown in Parentheses) for Regression Coefficients in Linear Models Testing the Relationship Between Hair and Blood Aluminum Levels With BSID Scores*

	Hair Aluminum (Wald Statistic) *P*		Blood Aluminum (Wald Statistic) *P*	
Score	All Data (N = 85)	Extreme Outliers Excluded (n = 84)	All Data (N = 85)	Extreme Outliers Excluded (n = 77)
Cognitive composite	.23	.34	.62	.34
Language composite	.64	.83	.15	.68
Receptive communication	.52	.56	.19	.59
Expressive communication	.22	.46	.24	.84
Motor composite	.07 (3.5)	.02 (5.88)†	.95	.40
Fine motor	.10	.11	.88	.71
Gross motor	.17	.04 (4.38)†	.87	.41
Social emotional composite	.44	.81	.73	.31
General adaptive composite	.15	.14	.87	.23

BSID indicates Bayley Scales of Infant and Toddler Development, 3rd Edition.

The motor composite score for the infant with the outlying hair aluminum value was 91, which is below the 25th percentile for the motor composite score (25th percentile is 97). The gross motor score for the infant with the outlying hair aluminum value was 5, which is below the 25th percentile for the gross motor score (25th percentile was 7).

*Relationships between aluminum levels and BSID scores were not significantly confounded by age, sex, race/ethnicity, family income, or blood lead level.

†Statistically significant at $P < .05$.

Neither B-Al nor H-Al was correlated with age, suggesting that biomarker levels were constant among this cross-section of infants aged 9 to 13 months. No correlation was found between H-Al or B-Al concentrations and the infant's history of receipt of aluminum-containing immunizations, either the estimated cumulative aluminum load from previous immunizations or that from vaccines received on the date of testing. These results are similar to those reported by investigators who studied 15 premature infants before and after they received 1200 μg aluminum in their 2-month-old immunizations and reported no changes in blood or urine aluminum levels.[21]

One previous study reported excessive aluminum loading in premature infants receiving intravenous fluids[22]; another reported adverse neurodevelopmental effects of high aluminum exposure among premature infants receiving parenteral nutrition.[7] In our study of healthy infants we found no correlation between B-Al and BSID scores. Models excluding extreme outliers yielded significant inverse correlations between H-Al and motor composite and gross motor scores.

Our results should be interpreted with caution. Findings may not be generalizable as enrollment was confined to 1 urban primary care site with high numbers of minority families of lower socioeconomic status. The cross-sectional design prevented assessment of temporality. We studied a single age range of infants. Longitudinal studies, comparing repeated measures of biomarkers of aluminum exposure with measures of infant developmental progress, are needed.

CONCLUSION

In this study we found no correlation between infant B-Al or H-Al levels and immunization history. The significance of a correlation between H-Al and motor development should be assessed in a larger study.

ACKNOWLEDGMENTS

Financial disclosure: Supported by the Gerber Foundation (to A.D.W. and M.P.K.) and the Agency for Toxic Substances and Disease Registry (ATSDR), cooperative agreement award number 1U61TS000238-01 (to the Region 1 New England Pediatric Environmental Health Specialty Unit). The contents of this report are the responsibility of the authors and do not necessarily represent the official views of the ATSDR. The US Environmental Protection Agency supports the Pediatric Environmental Health Specialty Units by providing funds to ATSDR under Inter-Agency Agreement number DW-75-92301-05. Neither the US Environmental Protection Agency nor the ATSDR endorse the purchase of any commercial products or services mentioned in Pediatric Environmental Health Specialty Units publications. The Gerber Foundation, ATSDR, and US Environmental Protection Agency did not play any role in the design of this study; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the report for publication.

REFERENCES

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On-time Vaccine Receipt in the First Year Does Not Adversely Affect Neuropsychological Outcomes

WHAT'S KNOWN ON THIS SUBJECT: An increasing number of parents are concerned that children receive too many vaccines too soon, and some are requesting alternative immunization schedules. This practice is not evidence-based and may lead to increased incidence of vaccine-preventable diseases.

WHAT THIS STUDY ADDS: This is the first study to compare long-term neuropsychological outcomes between children with timely vaccination and those with delayed or incomplete vaccination. These data suggest that there is no benefit in delaying immunizations during the first year of life.

abstract

FREE

OBJECTIVES: To determine whether children who received recommended vaccines on time during the first year of life had different neuropsychological outcomes at 7 to 10 years of age as compared with children with delayed receipt or nonreceipt of these vaccines.

METHODS: Publicly available data, including age at vaccination, from a previous VaccineSafety Datalink study of thimerosal exposure and 42 neuropsychological outcomes were analyzed. Vaccine receipt was defined as timely when each vaccine was received within 30 days of the recommended age. Associations between timeliness and each outcome were tested in univariate analyses. Multivariable regression models were constructed for further assessment of the impact of timeliness on neuropsychological outcomes after adjustment for potential confounders. Secondary analyses were performed on a subset of children with the highest and lowest vaccine exposures during the first 7 months of life.

RESULTS: Timely vaccination was associated with better performance on 12 outcomes in univariate testing and remained associated with better performance for 2 outcomes in multivariable analyses. No statistically significant differences favored delayed receipt. In secondary analyses, children with the greatest vaccine exposure during the first 7 months of life performed better than children with the least vaccine exposure on 15 outcomes in univariate testing; these differences did not persist in multivariable analyses. No statistically significant differences favored the less vaccinated children.

CONCLUSIONS: Timely vaccination during infancy has no adverse effect on neuropsychological outcomes 7 to 10 years later. These data may reassure parents who are concerned that children receive too many vaccines too soon. *Pediatrics* 2010;125:1134–1141

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KEY WORDS

vaccines, vaccine safety, neurodevelopmental, public health

ABBREVIATIONS

VSD—Vaccine Safety Datalink
DT—diphtheria-tetanus-pertussis
Hib—*Haemophilus influenzae* type B

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Childhood vaccines have led to remarkable reductions in child mortality and disease-related injury during the past 60 years[1]; however, as the visible threats of vaccine-preventable diseases have decreased, parental concerns about vaccine safety have increased.[2] Most recently, these concerns have focused on the now debunked links between autism and the measles-mumps-rubella vaccine as well as concerns about the ethyl mercury–containing preservative thimerosal, which is no longer present in routine childhood immunizations except for some influenza vaccines.[3]

Another area of parental angst relates to potential overburdening of the infant immune system or other harms as a result of administration of multiple vaccines at an early age.[4] Although the number of parents who completely refuse vaccines remains low,[5] many families are requesting alternative immunization schedules that space out and delay receipt of the recommended childhood vaccines.[6] There is no evidence that timely receipt of all recommended vaccines during infancy causes harm of any type. Vaccine delay, conversely, may lead to potentially severe negative consequences as a result of prolonged susceptibility to vaccine-preventable diseases.[7] Nonetheless, misinformation in the media and on the Internet may increase parental demand for immunization schedules that vary substantially from national recommendations.

Because undervaccinated children in the United States have higher rates of some vaccine-preventable disease than vaccinated children,[8] randomized, controlled trials designed to assess the safety of recommended versus alternative immunization schedules cannot be conducted on ethical grounds; however, the National Vaccine Advisory Committee Vaccine Safety Working Group has suggested that retrospective observational studies of populations with natural variation in vaccination schedules may provide useful information on this issue.[9]

The Vaccine Safety Datalink (VSD) project has provided important safety information for a number of childhood vaccines[10–12] and has also been used to assess vaccine timeliness.[13,14] One recent VSD study found no evidence to support a causal association between thimerosal exposure during the first 7 months of life and neuropsychological outcomes at 7 to 10 years of age.[15] We used publicly available data from this study to evaluate whether children who received all recommended vaccines on time in the first year of life had different neuropsychological outcomes as compared with children with delayed receipt or nonreceipt of these vaccines.

METHODS

Data Source

A publicly available cohort of 1047 children from a previous study of thimerosal exposure and neuropsychological outcomes at 7 to 10 years was analyzed.[15] Children in the cohort were born between 1993 and 1997 and underwent 42 in-depth neuropsychological tests between 2003 and 2004. The public-use data set contains age in days for all vaccines administered during the first year of life. These data were used to construct timeliness variables. In addition to immunization history, the data set contains detailed sociodemographic and medical history data, which were used as covariates. The study was granted exempt status by the institutional review board at the University of Louisville.

Study Definitions

On the basis of the 1993–1997 immunization schedules,[16,17] children were required to have received at least 2 hepatitis B, 3 diphtheria-tetanus-pertussis (DTP), 3 *Haemophilus influenzae* type B (Hib), and 2 polio vaccines (2:3:3:2 series) to be considered up-to-date during the first year of life. For our primary analyses which used data from all children in the data set, vaccine receipt was defined as timely when each of these vaccine doses was received within 30 days of the recommended age, consistent with previous studies of vaccine timeliness.[18] Children who did not meet this definition were classified as having untimely vaccine receipt. Although receipt of 2 doses of 1 specific Hib vaccine (PRP-OMP) could complete the primary series, we required 3 doses of Hib vaccine for definitions of timeliness and up-to-date status to maximize the vaccine exposure, because both the number and the timeliness of vaccines received were components of dosage exposure for our analyses.

A second set of analyses were performed to measure more precisely the association between density of vaccine receipt and neuropsychological outcomes. In these analyses, we first stratified children by age in quintiles at completion of the 2:3:3:2 series. Children in the first 2 quintiles were considered to be the "most timely vaccinated" having received a minimum of 10 vaccines in the first 7 months of life. A "least vaccinated" group was defined as those in the cohort who received ≤6 vaccine doses of any type during the first 7 months of life (defined as ≤209 days). Although a small number of these children may have gone on to complete the 2:3:3:2 series before their first birthday, we included them in the least vaccinated group because they had the lowest density of vaccine receipt in the first 7 months of life.

Outcomes

The 42 specific neuropsychological tests have been previously described in detail.[15,19] In summary, these include assessments of speech and language,

verbal memory, achievement, fine motor coordination, visuospatial ability, attention and executive-functioning tasks, behavior regulation, tics, and general intellectual functioning. These tests were chosen on the basis of previous studies of neurodevelopmental outcomes associated with methylmercury exposure.[20,21]

Statistical Analyses

Associations between timeliness and each of the 42 outcomes were tested in univariate analysis by using *t* tests. Multivariable regression models were constructed to assess further the impact of timeliness on neuropsychological outcomes after adjustment for potential confounders. All analyses controlled for age, gender, birth weight, poverty status, maternal IQ, maternal education, study site, cumulative ethyl mercury exposure during the first 7 months of life, and Home Observation for Measurement of the Environment score (an objective assessment of stimulation and emotional support in the home environment, which has been associated with developmental outcomes).[22,23] Additional covariates that were associated with specific outcomes in the original study were included where appropriate (Supplemental Appendix, which is published as supporting information at http://pediatrics.aappublications.org/cgi/content/full/peds.2009-2489/DC1).[19] In the secondary analyses, outcomes were compared between the most timely and least timely vaccinated children by using *t* tests. Multivariable analyses were performed by using the same covariates as in the primary analyses. All statistical analyses were performed by using Stata 9.0 (Stata Corp, College Station, TX) and SPSS 17 (SPSS, Inc, Chicago, IL).

RESULTS

A total of 491 (47%) of 1047 children met the study definition for timely receipt. An additional 235 (23%) received all recommended vaccines during the study period but not on time. The remaining 311 (20%) did not receive all recommended vaccines during the study period. Timely receipt of individual vaccine series was highest for hepatitis B (83%) and polio (79%) vaccines and lowest for DTP (65%) and Hib (53%) vaccines. Type of vaccine could be verified for 2636 (93%) of 2834 Hib doses. Of these, only 15 (0.6%) were PRP-OMP. Nine (0.86%) children received no vaccines at all during the study period.

Selected characteristics of children in each group are presented in Table 1. Consistent with the study definitions, children in the untimely and least timely groups received fewer vaccines, both during the first year of life and the first 7 months of life. Children with later vaccine receipt had lower family household incomes in both analyses, although all groups averaged well above the poverty level. They also had lower percentages of mothers with college degrees. Finally, there were greater proportions of male children and single-parent households in the less timely groups. These differences did not reach statistical significance in the primary analyses of timely versus untimely receipt but did in the secondary analyses of most timely versus

TABLE 1 Selected Sociodemographic and Clinical Characteristics by Timeliness Status

Characteristic	Total Cohort ($N = 1047$)	Primary Analysis			Secondary Analysis		
		Untimely ($n = 556$)	Timely ($n = 491$)	P[a]	Least Timely ($n = 112$)	Most Timely ($n = 310$)	P[a]
Total no. of vaccines during first year of life, mean ± SD	10.90 ± 1.94	10.10 ± 2.34	11.80 ± 0.60	<.001	7.40 ± 3.49	11.80 ± 0.64	<.001
Total no. of hepatitis B vaccines during first year of life, mean ± SD	2.71 ± 0.77	2.46 ± 0.96	2.99 ± 0.27	<.001	1.68 ± 1.28	2.98 ± 0.30	<.001
Total no. of Hib vaccines during first year of life, mean ± SD	2.71 ± 0.64	2.42 ± 0.75	3.02 ± 0.17	<.001	1.88 ± 1.05	3.04 ± 0.21	<.001
Total no. of DTP/DTaP vaccines during first year of life, mean ± SD	2.85 ± 0.53	2.71 ± 0.69	3.01 ± 0.10	<.001	1.96 ± 0.98	3.01 ± 0.11	<.001
Total no. of polio vaccines during first year of life, mean ± SD	2.62 ± 0.61	2.51 ± 0.70	2.73 ± 0.46	<.001	1.86 ± 1.00	2.74 ± 0.46	<.001
Total no. of vaccines during first 7 mo of life, mean ± SD	9.4 ± 2.44	8.00 ± 2.41	11.10 ± 1.01	<.001	4.20 ± 1.96	11.20 ± 0.79	<.001
Age at assessment, mean ± SD, y	9.30 ± 1.08	9.40 ± 1.04	9.20 ± 1.11	<.001	9.20 ± 1.02	9.20 ± 1.15	.808
Male gender, %	48.6	51.0	45.8	.090	58.0	46.5	.036
Household income, mean ± SD[b]	412 ± 260	380 ± 241	448 ± 275	<.001	334 ± 217	448 ± 288	<.001
Maternal college degree, %	51.5	46.8	56.8	.001	42.9	58.4	.005
Single-parent household, %	19.5	21.5	17.1	.068	29.5	18.1	.011
HOME score, mean ± SD	12.00 ± 1.95	11.90 ± 1.98	12.10 ± 1.90	.070	11.90 ± 2.00	12.10 ± 1.95	.297

HOME indicates Home Observation for Measurement of the Environment.

[a] Calculated by using *t* tests.

[b] Reported as percentage above poverty level.

least timely receipt. There were no significant differences between the groups in the average Home Observation for Measurement of the Environment score.

In the primary analyses, timely receipt was significantly associated with better performance on 12 of 42 outcomes in univariate analyses (Table 2). Specifically, children with timely receipt scored statistically better on the Boston Naming Test, grooved pegboard, metacognition, and teacher Connor's ratings for hyperactivity and inattentiveness. They also had higher verbal, performance, and full-scale IQs and were reported by parents to stutter less than children with untimely receipt. Children with untimely receipt did not perform better (no clinically or statistically significant differences) on any of the outcomes.

Timely receipt remained independently associated with 2 outcomes in multivariable analysis (Table 3). Children who received their vaccines on time scored 1 point higher on the Developmental Neuropsychological Assessment (NEPSY) speeded naming test (mean: 27.4 [SD: 8.12]), which requires rapid access to and production of recurring colors, sizes, and shapes. They also scored 2.7 points higher on the Wechsler Abbreviated Scale of Intelligence performance IQ (standardized mean: 100 [SD: 15]), which assesses block design and matrix reasoning.

In the secondary analyses, children were separated into 3 groups (Fig 1). The most timely group ($n = 310$) completed the 2:3:3:2 series between 154 and 191 days (<6.4 months). The least timely group ($n = 112$) included 93 children who did not complete the series during the first year of life and 19 children who completed the series between 263 and 363 days. All children who were not categorized into the most or least timely group ($n = 625$) were excluded from the secondary analyses. Univariate comparisons between the most and least timely vaccinated children are presented in Table 2. Children in the most timely group performed statistically better than children in the least timely group for 15 of the 42 outcomes, including 10 of the 12 outcomes associated with better outcome in the primary analysis. No test differences favoring the least timely group reached statistical significance. There were no significant differences between the 2 groups for any of the outcomes in multivariable analysis.

DISCUSSION

Receipt of all recommended childhood vaccines on time in the first year of life in 1993–1997 had no negative impact on neuropsychological outcomes at 7 to 10 years of age, compared with delayed receipt or nonreceipt of ≥1 dose during infancy. In fact, children who received each dose of each vaccine on time performed better on 2 of the 42 outcomes tested after adjustment for multiple familial and socioeconomic factors. Those with delayed receipt or nonreceipt of ≥1 infant dose did not perform better on any measure.

We initially analyzed vaccine dose exposure as a simple dichotomous timeliness variable on the basis of the Centers for Disease Control and Prevention's immunization schedule: receipt of each recommended dose on time versus ≥1 dose being delayed or missing. This definition of timeliness, however, was initially developed to identify factors that are associated with undervaccination and ongoing susceptibility to vaccine-preventable diseases.[18] Use of this strict definition classified children who completed the 2:3:3:2 series within the first 7 or 8 months of life as untimely when any of the doses were given outside of the 30-day window from earliest date of eligibility. This accounts for the relatively small differences in the mean number of vaccine doses received in the first 7 months of life between the timely and untimely groups (11 vs 8), which might have masked small but important differences on ≥1 test outcome.

To address more precisely the issue of density of vaccine exposure in the first 7 months of life as a potential risk factor for poorer neurodevelopmental outcomes, we identified a subset of children who had maximum receipt of vaccines during the first 7 months of life (mean: 11.2 doses) and a subset of children who had least timely vaccination and far less exposure to vaccines during the first 7 months of life (mean: 4.2 doses). The least timely vaccinated children did not perform better than the most timely vaccinated children for any of the 42 assessments. The most timely children performed better on 15 of 42 measures in univariate analyses, but these differences did not persist in multivariable analyses. Differences in familial and socioeconomic factors between the 2 groups likely accounted for the univariate results.

This comparison of the subsets of most and least vaccine exposed confirmed the findings of the timely versus nontimely analyses of the full cohort. In both analyses, the comparison groups received multiple patterns of vaccination receipt, some of which were delayed but ultimately complete and others that were only partially to minimally complete. The lack of any statistically significant results that favored delayed receipt of vaccines in the first year of life sends a clear public health message that should be comforting to many parents with vaccine safety concerns: children can receive their immunizations on time and expect to have the same neurodevelopmental outcomes as children with any other pattern of vaccine receipt.

This is important because vaccine delay in the first year of life, regardless of

TABLE 2 Neuropsychological Outcomes Associated With Timely Vaccination in Univariate Analysis

Domain	Specific Outcome	Primary Analysis		Secondary Analysis	
		Untimely ($n = 556$)	Timely ($n = 491$)	Least Timely ($n = 112$)	Most Timely ($n = 310$)
Speech and language	Boston Naming Test[a,b]	39.1	40.1	37.4	40.3
	NEPSY				
	Speeded naming[b]	26.9	27.9	26.0	27.8
	Comprehension of instructions	23.5	23.6	23.6	23.7
	Clinical Evaluation of Language Fundamentals				
	Formulated sentences	32.7	32.9	32.2	33.1
	Recalling sentences	44.2	45.0	43.6	44.9
	Goldman-Fristoe Test of Articulation (lower = better)	1.58	1.56	1.66	1.51
	Stuttering, %				
	Rating by evaluator	3.24	3.48	2.70	3.24
	Rating by parent[a]	3.62	1.04	2.70	0.65
	Rating by teacher	9.36	8.47	7.69	9.32
Verbal memory	California Verbal Learning Test				
	Free recall				
	No delay	46.60	46.30	45.50	46.70
	Short delay	9.81	9.64	9.66	9.62
	Long delay	10.40	10.40	9.90	10.40
	Cued recall				
	Short delay	10.3	10.3	9.7	10.3
	Long delay[b]	10.6	10.7	10.1	10.7
	Children's Memory Scale				
	Immediate recall	48.2	46.4	45.3	46.5
	Delayed recall	45.2	43.7	41.4	43.7
Achievement	Woodcock-Johnson III (letter and word identification)[b]	50.9	50.9	47.8	51.2
Fine motor coordination	Grooved pegboard (lower = better)				
	Dominant hand[a,b]	69.1	62.2	67.7	60.7
	Nondominant hand[a,b]	77.5	69.3	77.8	67.4
	Finger tapping				
	Dominant hand	38.9	38.7	37.5	38.6
	Nondominant hand	34.8	34.1	33.2	34.2
Visuospatial ability	Stanford-Binet copying test	18.1	18.3	17.8	18.4
Attention/executive functioning	Gordon Diagnostic System (vigilance task)				
	Correct responses	40.4	40.5	39.7	40.5
	Errors (lower = better)	8.3	6.7	8.3	7.0
	Wechsler Intelligence Scale (digit span)				
	Forward recall	8.09	8.01	8.05	7.99
	Backward recall[b]	4.52	4.54	4.16	4.56
	Combined	12.6	12.5	12.2	12.5
	Behavior Rating Inventory of Executive Function (metacognition index, lower = better)				
	Rating by parent[a,b]	75.4	73.0	76.9	73.0
	Rating by teacher[a,b]	69.3	64.9	72.7	65.4
Behavior regulation (lower = better)	Connor's Rating Scales				
	Hyperactive or impulsive				
	Rating by parent	5.46	5.38	5.80	5.05
	Rating by teacher[a,b]	4.40	3.47	5.38	3.42
	Inattentive				
	Rating by parent[b]	6.58	5.98	7.46	5.95
	Rating by teacher[a,b]	7.40	5.95	8.28	6.13
	Behavior Rating Inventory of Executive Function (behavioral regulation index)				
	Rating by parent	42.4	42.1	43.3	41.8
	Rating by teacher	39.5	38.0	40.4	37.7
Tics (lower = better)	Rating by evaluator, %				
	Motor tics	8.99	8.81	6.25	10.39
	Phonic tics	6.65	7.99	7.14	9.09
	Rating by parent, %				
	Motor tics	10.49	7.47	10.71	7.82
	Phonic tics	11.39	8.68	14.29	10.39
General intellectual functioning	Wechsler Abbreviated Scale of Intelligence				
	Verbal IQ[a,b]	106.0	108.9	105.1	108.7
	Performance IQ[a,b]	103.0	107.3	102.2	107.6
	Full-Scale IQ[a,b]	105.3	109.2	104.1	109.2

Average scores for continuous variables are summarized as means. The 7 dichotomous outcomes are summarized as percentages and are indicated as such in the table. Except where noted, higher score indicates better performance.

[a] $P < .05$ for an association between timely receipt and better outcome in primary analysis.

[b] $P < .05$ for an association between most timely receipt and better outcome in secondary analysis.

TABLE 3 Neuropsychological Outcomes Associated With Timely Vaccination in Multivariable Analysis

Outcome	Coefficient	95% CI	*P*
NEPSY speeded naming test	1.08	0.16–2.00	.022
WISC performance IQ	2.72	0.91–4.52	.003

Both analyses controlled for age, gender, birth weight, poverty status, Home Observation for Measurement of the Environment score, maternal IQ, maternal education, study site, computer experience, presence of siblings, use of English as primary language, duration of breastfeeding, prenatal fish exposure, iron deficiency, use of attention-deficit/hyperactivity disorder (ADHD) stimulants, and cumulative ethyl mercury exposure during the first 7 months of life. Additional covariates in the speeded naming test model include maternal age, participation in home-based child care, history of intrauterine growth restriction, prenatal exposure to nicotine, prenatal exposure to alcohol, prenatal exposure to tuna, prenatal exposure to organic mercury, maternal speech delay, maternal language delay, and maternal ADHD. CI indicates confidence interval; NEPSY, Developmental Neuropsychological Assessment; WISC, Wechsler Intelligence Scale for Children.

whether it is intentional, can have negative consequences. This is particularly true for pertussis, because disease incidence and mortality are highest in children who are younger than 6 months.[24] Furthermore, delayed receipt may lead to series noncompletion. For example, it is known that children who receive the third dose of diphtheria-tetanus-acellular pertussis (DTaP) late are less likely to receive a fourth dose of DTaP.[25]

We used individual vaccine doses as the unit of dosage exposure rather than estimating total or cumulative antigenic exposure. Some antigens are more reactogenic than others in the first day or 2 after injection, but how such "short-term" differences may or may not translate or relate to any differences in neurologic or immunologic development are unknown. However, our most timely group had the maximum possible vaccine antigen exposures during their infancies, whereas the least vaccinated comparison group had <40% (on the basis of vaccine doses) of this exposure.

Delays in receipt of childhood vaccines may be nonintentional (eg, poor access to care, accession of care) or attributable to parental request. Nonintentional delays are known to be associated with maternal marital status (single), lower maternal education, and family socioeconomic status.[5,18] We found similar associations between timeliness of vaccine receipt and these factors in this health maintenance organization–based population, although <2% of the children in the cohort had family incomes below the federal poverty level. In contrast, only 1 of the 9 children who had not received any vaccines resided in a single-parent household, and 6 had mothers with college degrees. This is consistent with a previous study that demonstrated that children who received no vaccines are more likely to come from affluent, well-educated families.[5] This cohort did not have enough children who were fully unvaccinated in the first year of life to form robust estimates of neuropsychological outcomes as compared with children with other patterns of receipt. This is an inherent limitation of any VSD-based study given the generally high immunization rates of children within the member health maintenance organizations.[26] We did not attempt to control statistically for potential differences between completely unvaccinated children and those with late receipt.

A notable strength of this analysis is that the initial study ascertained many important familial and socioeconomic covariates for the neurodevelopmental outcomes. The outcomes also were measured with blinding to the vaccine histories of the children. In addition, the sample size of the initial study was substantial, allowing us ample power to detect small but meaningful differences, even in our subgroup analyses. For example, we had 86% power (posthoc analysis) to detect a 5-point difference in IQ measures as statistically significant (2-sided $\alpha = .05$). Such results, even a 3-point difference (in favor of on-time vaccination), were detected as significantly different in univariate testing. Thus, it is unlikely that a protective effect of delayed vaccination truly exists but was undetected in these analyses. Nevertheless, as with any nonrandomized study, it is possible that we did not fully adjust for confounders that were not present in the original study and may have biased the association between timely vaccination and the outcomes of interest. Given the favorable associations between timely vaccination and most outcomes in the univariate analyses, it seems unlikely that true net adverse

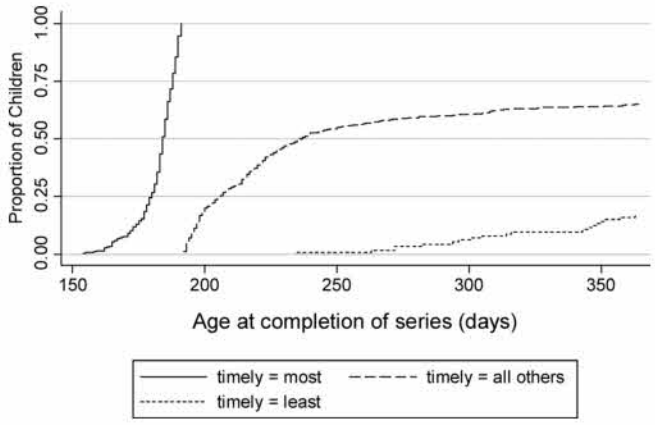

FIGURE 1
Up-to-date status in the study cohort. Only children in the most and least timely vaccinated groups were included in the secondary analyses.

effects have been masked by unmeasured or unevaluated confounders; however, there may be alternative study designs that more accurately assess associations between time-dependent exposures and outcomes in retrospective studies. We are exploring the use of other methods, including survival and propensity-adjusted analyses, for future studies of outcomes associated with vaccine timeliness.

Because the children in this study were born between 1993 and 1997, these results may not be generalizable to the current infant immunization schedule, which now includes 3 doses of heptavalent pneumococcal conjugate vaccine, 3 doses of oral rotavirus vaccine, and 1 or 2 doses of influenza vaccine in the first year of life (earliest eligibility at 6 months of age). This limitation is presently unavoidable in any vaccine safety study with long-term follow-up. However, most of the children in this study received DTP rather than DTaP, so the total antigenic burden to which children in this study cohort were exposed was actually higher than that encountered by children today.[27] Finally, our analyses were limited to publicly available data from the original study. Future VSD studies without this restriction would be able to assess a wider range of outcomes. These include putative vaccine adverse effects such as neurodevelopmental delay, autism, and autoimmune disorders. The association between vaccine timeliness and the incidence of vaccine-preventable diseases could also be measured.

CONCLUSIONS

This study provides the strongest clinical outcomes evidence to date that on-time receipt of vaccines during infancy has no adverse effect on neurodevelopmental outcomes 7 to 10 years later. These results offer reassuring information that physicians and public health officials may use to communicate with parents who are concerned that children receive too many vaccines too soon.

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BPA Controversy Continues: *While there has been much in the news recently about the potential dangers of bisphenol A (BPA) resulting in recommendations to avoid products such as baby bottles and canned goods lined with it, the Food and Drug Administration continues to note that this chemical does not pose a risk at low levels of human exposure. Those against BPA argue that we don't know what a low level really is, and those who don't see it as a problem are calling for more research to disprove the fears. According to an editorial in the* The Wall Street Journal *(January 30, 2010), the National Toxicology Program filed a report in 2008 noting some concern for effects of BPA on the brain, behavior, and prostate glands in fetuses, infants, and children. The other 320 pages to this report have largely been overlooked, despite their noting that these studies are controversial because they have not been successfully reproduced by independent investigators, study designs are questionable, the relevance of animal models for human risks is not clear, and we lack understanding of just what the potential adverse nature of reported effects are. While BPA has been called an "endocrine disruptor" because it binds to estrogen receptors, the National Toxicology study states, "there is currently no evidence that estrogen receptor signaling plays an essential role in male-typical brain and behavioral sexual differentiation" in humans. The National Institute of Environmental Health Sciences is currently investing $30 million in further BPA research. Hopefully the findings will allow us to put the cap on the bottle in terms of whether or not we really need to worry about BPA.*

Noted by JFL, MD

On-time Vaccine Receipt in the First Year Does Not Adversely Affect Neuropsychological Outcomes

Michael J. Smith and Charles R. Woods

Pediatrics 2010;125;1134
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Increasing Exposure to Antibody-Stimulating Proteins and Polysaccharides in Vaccines Is Not Associated with Risk of Autism

Frank DeStefano, MD, MPH[1], Cristofer S. Price, ScM[2], and Eric S. Weintraub, MPH[1]

Objective To evaluate the association between autism and the level of immunologic stimulation received from vaccines administered during the first 2 years of life.

Study design We analyzed data from a case-control study conducted in 3 managed care organizations (MCOs) of 256 children with autism spectrum disorder (ASD) and 752 control children matched on birth year, sex, and MCO. In addition to the broader category of ASD, we also evaluated autistic disorder and ASD with regression. ASD diagnoses were validated through standardized in-person evaluations. Exposure to total antibody-stimulating proteins and polysaccharides from vaccines was determined by summing the antigen content of each vaccine received, as obtained from immunization registries and medical records. Potential confounding factors were ascertained from parent interviews and medical charts. Conditional logistic regression was used to assess associations between ASD outcomes and exposure to antigens in selected time periods.

Results The aOR (95% CI) of ASD associated with each 25-unit increase in total antigen exposure was 0.999 (0.994-1.003) for cumulative exposure to age 3 months, 0.999 (0.997-1.001) for cumulative exposure to age 7 months, and 0.999 (0.998-1.001) for cumulative exposure to age 2 years. Similarly, no increased risk was found for autistic disorder or ASD with regression.

Conclusion In this study of MCO members, increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines during the first 2 years of life was not related to the risk of developing an ASD. *(J Pediatr 2013;163:561-7).*

The initial concerns that vaccines may cause autism were related to the measles, mumps, and rubella vaccine[1] and thimerosal-containing vaccines.[2] In 2004, a comprehensive review by the Institute of Medicine concluded that the evidence favors rejection of possible causal associations between each of these vaccine types and autism.[3] Nonetheless, concerns about a possible link between vaccines and autism persist,[4] with the latest concern centering on the number of vaccines administered to infants and young children.[5] A recent survey found that parents' top vaccine-related concerns included administration of too many vaccines during the first 2 years of life, administration of too many vaccines in a single doctor visit, and a possible link between vaccines and learning disabilities, such as autism.[6] All of the foregoing concerns were reported by 30%-36% of all survey respondents, and were reported by 55%-90% of parents who indicated that their children would receive some, but not all, of the vaccines on the recommended schedule. Another recent survey found that more than 10% of parents of young children refuse or delay vaccinations, with most believing that delaying vaccine doses is safer than providing them in accordance with the Centers for Disease Control and Prevention's recommended vaccination schedule.[7]

Using the number of antibody-stimulating proteins and polysaccharides contained in vaccines as a measure, we evaluated the association between the level of immunologic stimulation received from vaccines during the first 2 years of life and the risk of developing an autism spectrum disorder (ASD), including specific ASD subtypes.

Methods

We performed a secondary analysis of publicly available data from a case-control study designed to examine potential associations between exposure to thimerosal-containing injections and ASD.[8] The study was conducted in 3 managed care organizations (MCOs). Data sources for the original study included MCO computerized data files, abstraction of biological mothers' and children's medical charts, and standardized telephone interviews with biological mothers. Case children underwent standardized in-person assessment to verify case status.

AD	Autistic disorder
ADI-R	Autism Diagnostic Interview–Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism spectrum disorder
MCO	Managed care organization
SCQ	Social Communication Questionnaire

From the [1]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA and [2]Abt Associates Inc, Bethesda, MD

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Further details regarding study design, analyses, and results are available elsewhere.[9,10] The original study received Institutional Review Board approvals from all participating institutions; the present analysis was determined to be exempt from additional Institutional Review Board review.

For each of 3 age ranges (birth to 3 months, birth to 7 months, and birth to 2 years), we evaluated the associations between the total cumulative exposure to antibody-stimulating proteins and polysaccharides from childhood vaccinations and 3 outcomes: ASD, autistic disorder (AD), and ASD with regression. We also evaluated associations with the maximum number of antigens to which a child was exposed in a single day.

Study-eligible children were: (1) born between January 1, 1994, and December 31, 1999; (2) had been continuously enrolled in the MCO from birth until their second birthday; and (3) were currently enrolled at the time of sample selection. The children were aged 6-13 years at the time of data collection. Parents provided written consent for study participation. Children were excluded who had any the following medical conditions with known links to ASD traits: fragile X syndrome, tuberous sclerosis, Rett syndrome, congenital rubella syndrome, or Angelman syndrome. Control children were selected at random from the MCO populations to match cases within matching strata defined by birth year, sex, and MCO.

Potential cases were identified by searching the MCO computerized records for relevant *International Classification of Diseases, Ninth Revision* codes for ASD (299.0-ASD or 299.8-PDD NOS), supplemented by text string searches at 1 MCO and by text strings and autism registries at another. Mothers of case children were administered the Autism Diagnostic Interview–Revised (ADI-R),[11] and case children were assessed directly by trained assessors using the Autism Diagnostic Observation Schedule (ADOS).[12]

ASD consists of qualitative abnormalities in reciprocal social interactions and communication, along with restrictive, repetitive, and stereotyped patterns of behavior. Children meeting study criteria for ASD had ADOS scores indicating abnormalities in all 3 areas and had ADI-R scores indicating abnormalities in reciprocal social interactions and either communication or patterns of behavior. The children meeting study criteria for AD were a subset of children with ASD who had higher scores on all 3 areas of the ADOS, ADI-R scores indicating abnormalities in all 3 areas, and onset before age 36 months. Using items from the ADI-R, ASD with regression was defined as the subset of children with ASD who reported loss of previously acquired language skills after acquisition. Assessors were blinded to the vaccination histories of study children.

To reduce the likelihood that the control group included children with undiagnosed ASD, the Lifetime form of the Social Communication Questionnaire (SCQ)[13] was administered as part of the maternal interview in children with signs of neurodevelopmental difficulties. Seven control group children with an SCQ score >15 were excluded from the analysis.

Table I. Number of antibody-stimulating protein and polysaccharide antigens in vaccines and number of vaccine doses administered according to type of vaccine

Vaccine type	Antigens per dose	Doses*
DT/TD	2	14
DTP	3002	235
DTP-Hib	3004	1659
DTaP	4†	1165
DTaP	5†	789
DTaP	6†	492
DTaPHepB	6†	3
Influenza	10	95
Hib	2	2123
HepA	4	22
HepB	1	3085
HepB-Hib	3	215
MMR	24	1093
Measles	10	2
Meningococcus‡	2	285
Mumps	9	1
Pneumococcus§	8	698
Polio	15	3385
Rabies	5	1
Rotavirus¶	14	57
Rubella	5	2
Typhoid	3000	4
Varicella	69	917
Yellow fever	11	1

DT/TD, diphtheria and tetanus toxoids; *DTaP*, diphtheria, tetanus, and acellular pertussis; *DTP*, diphtheria, tetanus, and whole-cell pertussis; *HepA*, hepatitis A; *HepB*, hepatitis B; *Hib*, *Hemophilus influenzae* type B; *MMR*, mumps, measles, rubella.
*Total vaccine doses administered in the study population from birth to age 2 years.
†Number of antigens in DTaP vaccines varied by manufacturer.
‡Meningococcal C conjugate vaccine was administered as part of a clinical trial at 1 MCO.
§Pneumococcal conjugate (7-valent) vaccine; some doses were administered in a clinical trial at 1 MCO.
¶RotaShield Wyeth-Ayers, Philadelphia, Pennsylvania (no longer marketed).

We obtained the children's vaccination histories from computerized immunization tracking systems and abstracted medical charts. We adapted published data on the antibody-stimulating proteins and polysaccharides content of selected vaccines[14,15] to determine the antigen loads in the various vaccines (Table I).

We evaluated antigen exposure for 3 age ranges according to 2 measures: cumulative exposure to antigens within the specified age range and the maximum number of antigens received in a single day within the specified age range. Data were collected on a large number of covariates, including child and family characteristics, maternal exposures during pregnancy, childbirth conditions, early childhood health conditions, and maternal healthcare-seeking behavior (ie, Kotelchuck prenatal care index, cholesterol, and Pap smear screenings).[9]

For the primary statistical analysis, we fit conditional logistic regression models to estimate the ORs for ASD outcomes associated with a 1-unit increase in antigen exposure. To facilitate interpretation of the results, we present the estimated ORs for an increase of 25 antigen units (approximately the total number of antigens contained in diphtheria, tetanus, and acellular pertussis; inactivated polio vaccine; *Hemophilus influenzae* type B; and hepatitis B vaccines). We also performed analyses in which we categorized antigen exposure

into 3 levels, with the lowest level serving as the referent category for the 2 higher levels. All tests were 2-tailed, and statistical significance was set at $P < .05$.

Results

Of 771 potential cases and 2760 controls selected for recruitment, 103 cases (13.4%) and 316 controls (11.4%) were deemed ineligible.[9] Among the remaining 668 cases and 2444 controls, 321 cases (48.1%) and 774 controls (31.7%) participated in all phases of the study. Twelve of the 774 control participants (1.6%) were excluded because analysis of medical chart and parent interview data revealed exclusionary conditions. In addition, 10 controls were not included in the analysis because there were no cases in their matching strata. Of the remaining 752 controls included in the analysis, 186 had an SCQ score <16 but had indications of speech delay or language delay, learning disability, attention deficit hyperactivity disorder or attention deficit disorder, or tics, or had an individual education plan.

Of the 321 potential case children who participated in standardized assessments, 256 (79.8%) met study criteria for ASD. Among these 256 children, 187 (73%) met the stricter criteria for AD and 49 (19%) met the criteria for ASD with regression.

The children were aged 6-13 years at the time of data collection, and the group was 85% male. Birth weight distributions; maternal age, education, and marital status; and paternal age were similar for cases and controls.[8]

The distributions of cumulative antigen exposures for each of the 3 age ranges are shown in **Figure 1**. For both cases and controls in all 3 age groups, the cumulative exposures exhibited a bimodal distribution depending on receipt of whole-cell vaccines. For example, approximately one-half of the study children never received a whole-cell pertussis-containing vaccine or a typhoid vaccine during their first 7 months of life, and thus had cumulative exposures of 0-125 antigens during that period. In the birth to 7 months group, children who received a single whole-cell pertussis-containing vaccine (and possibly other vaccines) had cumulative exposures of 3000-3250 antigens, those who received 2 whole-cell pertussis-containing vaccines had cumulative exposures of 6000-6250 antigens, and those who received 3 whole-cell pertussis-containing vaccines had cumulative exposures of 9000-9250 antigens. In the birth to 2 years group, cumulative antigen exposures were 0-311 in children who received no whole-cell pertussis or typhoid vaccines and 3000-15 250 in those who received 1 or more whole-cell vaccines.

Maximum antigen exposures on a single day also exhibited a bimodal distribution depending on receipt of whole-cell pertussis or typhoid vaccines (**Figure 2**). In the birth to 7 months group, no child received more than 1 whole-cell pertussis-containing vaccine (or typhoid vaccine) in a single day; thus, no child was exposed to more than 3320 antigens in a single day. In the birth to 2 years group, 1 control child received a whole-cell pertussis-containing vaccine, a typhoid vaccine, and other vaccines in a single day, resulting in a maximum single-day exposure of 6112 antigens.

In the regression models, the risk of acquiring an ASD was not associated with total antigen exposure at birth to 3 months, birth to 7 months, or birth to 2 years (**Table II**). In the analyses with exposure categorized at 3 levels, the ORs all had 95% CIs that overlapped 1.0 (ie, were not statistically significant). The ORs for a 25-unit increase in vaccine antigen exposure, analyzed as a continuous variable and adjusted for several potential confounding variables, also revealed no significant increase in the risk of various ASD outcomes with increasing vaccine antigen exposure. Moreover, the risk of ASD was not associated with maximum antigen exposure on a single day (**Table III**). In a previous analysis,[8] we found that thimerosal exposure during certain time periods was associated with a decreased risk for some ASD outcomes; thus, we performed additional analyses in which thimerosal exposure was included as a covariate, and found little change from the results presented in **Tables II** and **III** (data not shown).

Because the antigen content of whole-cell pertussis-containing vaccines is much greater than other vaccines, we performed further analyses according to the number of whole-cell pertussis vaccine doses received. These analyses adjusted for the same covariates included in the 25-antigen increase models presented in **Tables II** and **III**. We found no statistically significant associations between number of whole-cell pertussis vaccine doses received between birth and age 2 years and any of the ASD outcomes; ORs (95% CI) for each increase of 1 whole-cell pertussis vaccine dose were 0.956 (0.793-1.152) for ASD, 0.989 (0.700-1.397) for AD, and 0.761 (0.380-1.525) for ASD with regression.

Discussion

We found no evidence indicating an association between exposure to antibody-stimulating proteins and polysaccharides contained in vaccines during the first 2 years of life and the risk of acquiring ASD, AD, or ASD with regression. We also detected no associations when exposures were evaluated as cumulative exposure from birth to 3 months, from birth to 7 months, or from birth to 2 years, or as maximum exposure on a single day during those 3 time periods. These results indicate that parental concerns that their children are receiving too many vaccines in the first 2 years of life or too many vaccines at a single doctor visit are not supported in terms of an increased risk of autism.

The present study evaluated the level of immunologic exposure from vaccines and the risk of autism. Smith and Woods[16] reported finding no association between the total number of infant vaccinations and several neurodevelopmental outcomes, but that study did not include autism. Their analysis implicitly assumed that all vaccines have equivalent antigenic loads. Offit et al[15] proposed that a more complete assessment of the antigenic content of

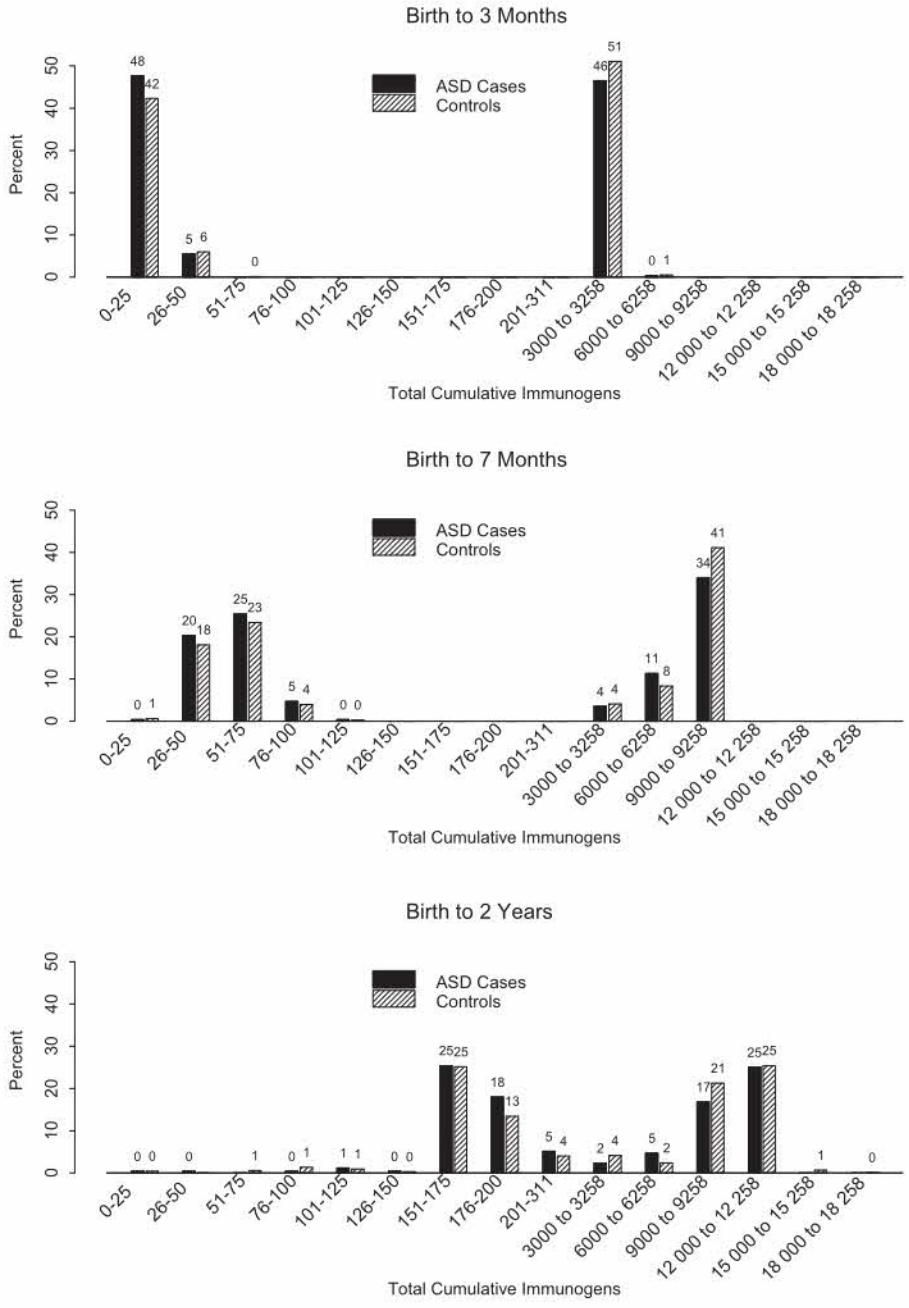

Figure 1. Distribution of total cumulative antigen exposure among ASD cases and controls, by age range.

vaccines should take into account all of the antibody-stimulating proteins and polysaccharides in each vaccine, which is the approach that we took in the present study. Admittedly, this approach assumes that all proteins and polysaccharides in a vaccine evoke equivalent immune responses, whereas some proteins actually may be more likely than others to stimulate an immune response.[14] Moreover, the calculations do not take into account the number of epitopes per antigen or the immunologic strength of each epitope. Nonetheless, we believe that our estimates provide a valid relative ranking of the antigen content of vaccines.

The immunization schedule in effect during the years in which our study children were vaccinated included some, such as diphtheria, tetanus, and whole-cell pertussis, that were cruder and more antigenic than current vaccines, and also caused more side effects. Removal of whole-cell pertussis vaccine from the childhood vaccination schedule has substantially decreased the antigenic load from vaccines. Thus, even though the routine childhood schedule in 2012 contains several more vaccines than the schedule in the late 1990s,[17] the maximum number of antigens to which a child could be exposed by age 2 years was 315 in 2012, compared with

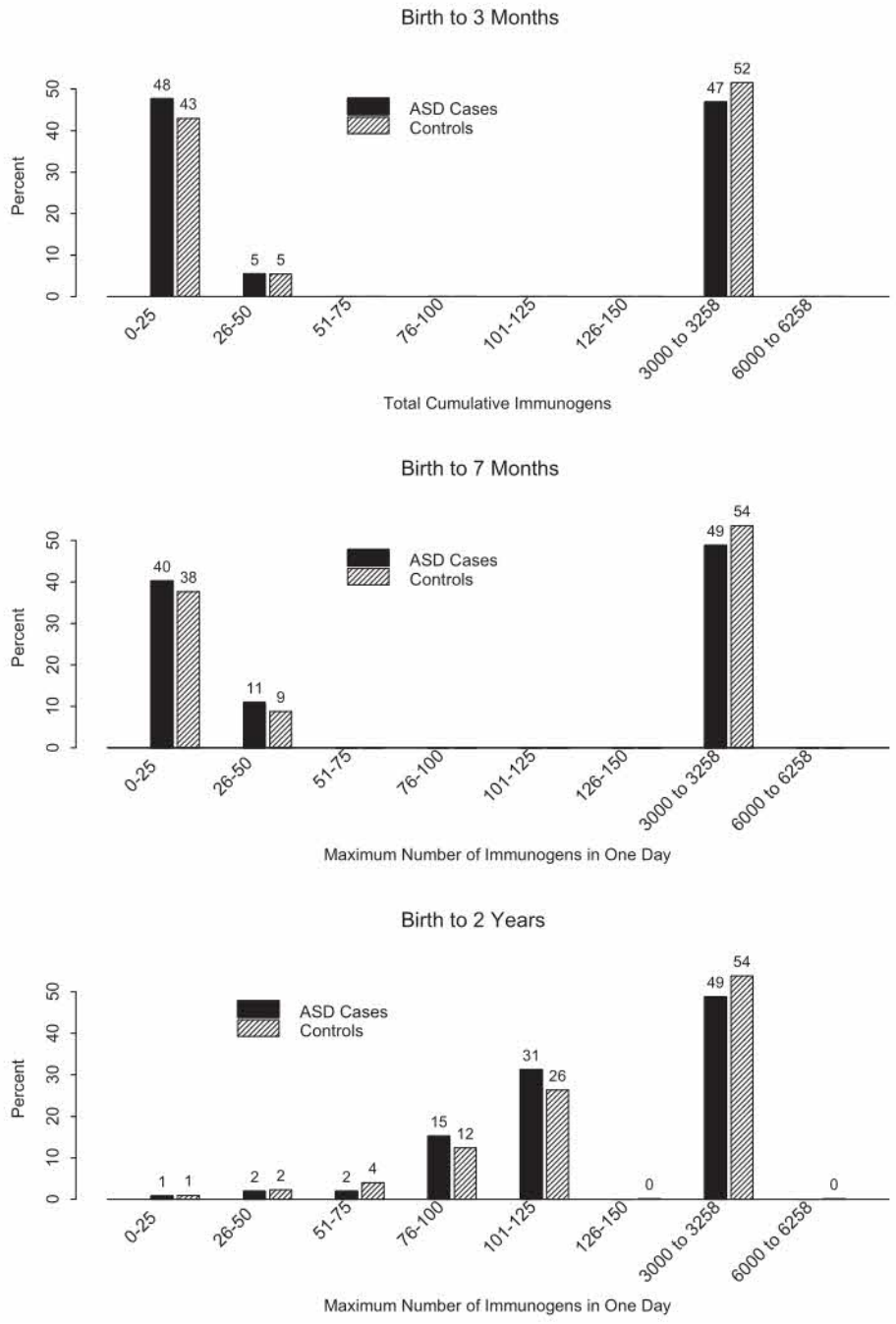

Figure 2. Distribution of maximum antigen exposure in a single day among ASD cases and controls, by age range.

several thousand in the late 1990s. Our results cover a broader range of vaccine antigen exposures than the typical child would be exposed to today, and thus our results provide relevant data for the current immunization schedule.

In addition to our measures of antigen content, the original study from which our analysis is derived had several other strengths. State-of-the-art assessment tools, including in-person observational assessments of case children, were used to validate diagnoses of ASD and subtypes of ASD. Data on childhood immunizations were derived from computerized immunization tracking systems and medical chart data sources and thus were not susceptible to recall bias. Extensive information on potential confounding factors was collected, and these factors were controlled for in the analysis. However, measures of prenatal and infant exposure to a number of risk factors were obtained from maternal interviews, and differential recall might have affected adjustments for potential confounding variables. This is a minor concern, given that covariate adjustment had little impact on the results.

Table II. Associations between cumulative vaccine antigen exposures and autism outcomes, according to selected age intervals

Exposure period and ASD outcome	Exposure categories by number of antigens, unadjusted OR (95% CI)			Continuous variables, aOR (95% CI), per 25-antigen increase*
Birth to 3 months	0-25	26-75	3000-6258	
ASD	1.0 (referent)	0.87 (0.41-1.82)	0.84 (0.47-1.51)	0.999 (0.994-1.003)
AD	1.0 (referent)	1.24 (0.56-2.72)	1.09 (0.56-2.11)	1.000 (0.995-1.005)
ASD with regression	1.0 (referent)	0.27 (0.03-2.27)	1.10 (0.38-3.19)	1.002 (0.993-1.010)
Birth to 7 months	0-125	3000-6258	9000-9258	
ASD	1.0 (referent)	0.96 (0.50-1.83)	0.74 (0.38-1.43)	0.999 (0.997-1.001)
AD	1.0 (referent)	0.92 (0.44-1.92)	0.77 (0.36-1.61)	1.001 (0.997-1.004)
ASD with regression	1.0 (referent)	0.95 (0.28-3.25)	1.01 (0.30-3.34)	0.999 (0.993-1.004)
Birth to 24 months	0-311	3000-9258	12 000-18 258	
ASD	1.0 (referent)	0.76 (0.41-1.40)	0.82 (0.40-1.71)	0.999 (0.998-1.001)
AD	1.0 (referent)	0.76 (0.37-1.53)	0.78 (0.34-1.81)	1.000 (0.997-1.003)
ASD with regression	1.0 (referent)	0.94 (0.31-2.86)	0.65 (0.16-2.64)	0.998 (0.992-1.004)

*Covariates for ASD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare- seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, alcohol use, folic acid use, viral infection, lead exposure), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for AD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare-seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, folic acid use), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for ASD with regression models included birth weight, maternal age, family income, maternal education level, and maternal exposures during pregnancy with the study child (ie, alcohol use).

Knowledge that a child had ASD would not likely have influenced the choice of vaccines, considering that none of the case children had an ASD diagnosis by age 7 months and few had a diagnosis before age 2 years. Some of the case children, however, might have exhibited indications of neurodevelopmental problems well before receiving an ASD diagnosis. How evidence of early neurodevelopmental delays would have affected our results is not clear; it might have resulted in lower vaccination levels if parents were concerned about vaccinating their children, or possibly higher vaccination levels through more frequent contact with the healthcare system.

A potential limitation of this study is the possibility that socioeconomic factors could be related to both receipt of vaccines and evaluations for an ASD diagnosis. Differences in socioeconomic factors likely did not confound our results, however, given that all children were members of MCOs in which routine infant and childhood immunizations were a covered benefit. Moreover, we adjusted for numerous socioeconomic factors. Another potential concern is that children who had an older sibling with autism might have been less likely to receive vaccinations because their parents were aware of the speculative link between vaccines and autism.[18] Only 5% of ASD cases and 2% of controls had an older sibling with autism,[10] and the results were not changed when these children were excluded from the analysis (data not shown).

Considerations of biological mechanisms should be taken into account when evaluating a possible association between autism and immunologic stimulation from vaccines early in life. The infant's immune system is capable of responding to a large number of immunologic

Table III. Associations between maximum exposure to vaccine antigens in 1 day and autism outcomes, according to selected age intervals

Exposure period and ASD outcome	Exposure categories by number of antigens, unadjusted OR (95% CI)			Continuous variables, aOR (95% CI), per 25-antigen increase*
Birth to 3 months	0-25 antigens	26-50 antigens	3000-3258 antigens	
ASD	1.0 (referent)	0.98 (0.47-2.08)	0.87 (0.49-1.54)	0.999 (0.994-1.004)
AD	1.0 (referent)	1.41 (0.64-3.13)	1.12 (0.58-2.16)	1.000 (0.995-1.006)
ASD with regression	1.0 (referent)	0.23 (0.03-2.43)	1.12 (0.39-3.25)	1.002 (0.993-1.011)
Birth to 7 months	0-25 antigens	26-50 antigens	3000-3258 antigens	
ASD	1.0 (referent)	1.48 (0.80-2.74)	0.93 (0.50-1.75)	1.000 (0.998-1.002)
AD	1.0 (referent)	1.56 (0.78-3.13)	0.94 (0.46-1.93)	0.999 (0.994-1.004)
ASD with regression	1.0 (referent)	0.54 (0.13-2.16)	0.89 (0.29-2.68)	1.000 (0.991-1.009)
Birth to 24 months	0-100 antigens	101-150 antigens	3000-6258 antigens	
ASD	1.0 (referent)	1.37 (0.84-2.24)	0.85 (0.45-1.61)	1.000 (0.998-1.001)
AD	1.0 (referent)	1.62 (0.93-2.82)	0.89 (0.43-1.85)	0.998 (0.993-1.003)
ASD with regression	1.0 (referent)	2.15 (0.81-5.72)	1.19 (0.35-4.00)	0.999 (0.990-1.009)

*Covariates for ASD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare-seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, alcohol use, folic acid use, viral infection, lead exposure), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for AD models included birth weight, maternal age, birth order, duration of breastfeeding, family income, maternal healthcare-seeking behavior (ie, Kotelchuck inadequacy of prenatal care, use of cholesterol screening, use of Pap smear screening), maternal exposures during pregnancy with the study child (ie, folic acid use), and early childhood health conditions (ie, anemia at age 6-30 months, pica before age 3 years). Covariates for ASD with regression models included birth weight, maternal age, family income, maternal education level, and maternal exposures during pregnancy with the study child (ie, alcohol use).

stimuli. Beginning at birth, an infant is exposed to hundreds of viruses and other antigens, and it has been estimated that an infant theoretically could respond to thousands of vaccines at once.[15] The possibility that immunologic stimulation from vaccines during the first 1-2 years of life could be related to the development of ASD is not well supported by the known neurobiology of ASD, which tends to be genetically determined with origins in prenatal development,[19-22] although possible effects in early infancy cannot be ruled out completely. It can be argued that ASD with regression, in which children usually lose developmental skills during the second year of life, could be related to exposures in infancy, including vaccines; however, we found no association between exposure to antigens from vaccines during infancy and the development of ASD with regression. ■

We thank Dr Paul Offit for his assistance in determining the antibody-stimulating protein and polysaccharide content of specific vaccines.

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Aleksandra Gołoś, Anna Lutyńska

ALUMINIUM-ADJUVANTED VACCINES – A REVIEW OF THE CURRENT STATE OF KNOWLEDGE

Department of Sera and Vaccines Evaluation
of the National Institute of Public Health – National Institute of Hygiene in Warsaw

ABSTRACT

Since decades aluminium formulations such as aluminium hydroxide and aluminium phosphate are widely used as adjuvants in vaccines for human use. They increase immune response induced by the vaccine antigens by mechanisms eg. a depot effect at the injection site, activation of the complement and stimulation of the macrophages.

Many studies, both case control ones and those performed *in vivo* on animal models, confirmed the safety of aluminium adjuvants even in vaccinated infants and children.

Although some of the aluminium-adjuvanted vaccines have certain limitations such as no Th1 reactivity and low stability at temperatures below 2ºC, its easy use, safety profile and low manufacturing costs confirm its suitability.

Key words*: vaccines, aluminium adjuvant, safety*

INTRODUCTION

Adjuvants are commonly used agents to augment the immune response induced with viral or bacterial inactivated vaccine antigens, bacterial toxoids or polysaccharides but not attenuated live viral ones.

Many studies have shown that adjuvant-containing vaccines are capable to efficiently increase and prolong the maintenance of antibody response comparing to the unadjuvanted equivalents (1). Adjuvants were proven to induce a repository or depot effect at the site of injection with slow releasing of the antigen which allow for targeting the antigen to antigen-presenting cells (APC), stabilize epitope conformation, stimulate the macrophages to induce retention and activation of lymphocytes and activate the complement (1, 2, 3). Their stimulatory properties are very practical as they allow to reduce the amount of antigen per human dose and the number of required doses in the vaccination schedule as well (4).

Recently, the concerns about safety of aluminium-adjuvanted vaccines have been frequently raised by media. It seems that aluminium attention have taken the place of thiomersal fear lowered lately by the competent international authorities statements and progressive elimination of thiomersal from most of the vaccines currently being in use.

Aluminium adjuvants were the first excipients that have been approved in the content of vaccines used in humans (5). By many decades they have successfully been used to enhance immune response to many vaccine antigens in order to improve the efficiency of vaccination. Aluminium hydroxide or aluminium phosphate have been the most common class of vaccine adjuvants, recognized as safe when used according to the recommended vaccination schedules (2). Nevertheless, its proven adjuvancity mechanisms are still not entirely understood (6). They are recognized as Th2 type response inducers, however with low potential to induce cell-mediated immunity or immunity to peptide antigens (3).

Firstly, aluminium adjuvants were used in the formulas of diphtheria, tetanus and pertussis vaccines and inactivated poliomyelitis vaccines and over time they have been introduced into newly developed vaccines such as hepatitis A and B and inactivated thick-borne encephalitis vaccines (2). Nowadays, most of the adjuvanted vaccines are adsorbed on aluminium hydroxide

and only some eg. meningococcal and pneumococcal conjugate ones are adsorbed on aluminium phosphate. The combination of these both is used rarely.

PHYSICAL AND CHEMICAL PROPERTIES OF ALUMINIUM ADJUVANTS

Aluminium adjuvants are often referred as "alum"-containing products, but this term should be rather avoided, as it refers to specific chemical compound, hydrated aluminium sulfate, which is not under scope of vaccine aluminium-containing adjuvant (7). Aluminium-containing vaccines are formulated by adsorption of a given antigen onto aluminium hydroxide or aluminium phosphate gels (8). Nevertheless, commonly used names of aluminium hydroxide or aluminium phosphate, do not exactly describe their structures. Aluminium hydroxide, as identified using X-rays crystallography, is a crystalline aluminium oxyhydroxide (AlO(OH)), and aluminium phosphate is an amorphous aluminium hydroxyphosphate $Al(OH)_x(PO_4)_y$ (9). They are prepared by exposing aqueous solution of aluminium ions under alkaline conditions in a well-defined and monitored chemical environment (2). An avidity of the association between adjuvant and antigen is affected by many factors, such as the form of aluminium salt, the physico-chemical properties of the antigen (including molecular weight), the mode of preparation of the antigen-adjuvant complex and pH of the chemical environment (10). The main difference between aluminium oxyhydroxide and aluminium hydroxyphosphate reffers to theirs point of zero charge (PZC) which is estimated at pH 11.0 and pH 4.0 – 5.5, respectively. PZC represents a pH value at which electrical charge density on a surface of a solid submerged in an electrolyte obtains value of zero. This feature decides on choice of the best adjuvant for a given vaccine antigen according the charge of the last one (6). Generally, an efficient adsorption of antigen depends on the pH value obtained between the isoelectric point (IEP) of the antigen and the PZC of the adjuvant, due to guarantee the opposite electrical charges and optimal levels of electrostatic attraction and adsorption (2). Thus, aluminium hydroxide at pH of 11.0 is preferable for adsorption of antigens with an acidic IEP and aluminium phosphate at pH 4.0 - 5.5 for antigens with alkaline IEP (11).

Selection of an appropriate adjuvant is important for the expected level of immunogenicity and finally for the effectiveness of the vaccine. In case of DNA vaccines, the use of aluminium hydroxide as an adjuvant resulted in decreased immunogenicity, while application of the aluminium phosphate instead, effectively enhanced the immune response (12, 13).

Despite aluminum-containing adjuvants are used on so frequently, they reveal some limitations. Traditional aluminium-adsorbed vaccines are frost sensitive and thus not lyophilized (2). Exposure of the adjuvanted vaccines to freezing temperatures causes irreversible breakage of the lattice made up of bonds between the adsorbent and antigen, resulting in compromised immunogenicity and increasing of the risk of adverse local reactions (14).

SAFETY OF ALUMINIUM - ADJUVANTED VACCINES

Aluminium-containing adjuvants were proved for no evidence of risk of carcinogenicity or teratogenicity (15). As very high doses of aluminium can be toxic, safe aluminium compounds concentrations limits were clearly defined as 2 mg/kg per day. It should be emphasized, that exposure to aluminium content in vaccines is substantially lower than exposure originating from a diet (16), despite the fact that aluminium compounds in vaccines do not pass through the gastrointestinal tract, which is a significant barrier (17).

In Europe, the maximum acceptable amount of aluminium in vaccines administered to humans, in accordance with the requirements of the actual edition of the European Pharmacopoeia is 1.25 milligrams per human dose.

Aluminium compounds in some circumstances may however cause an allergic response. The most commonly observed adverse reactions related to aluminium-adjuvanted vaccines include painful and itchy nodules and redness at the injection site, however they are usually mild and short-lived (15).

Meta-analysis study on adverse events reported after immunization with aluminium-containing DTP vaccines administered to children, showed no evidence that aluminium salts in vaccine contents cause any serious and long-lasting adverse events (18). Up to date, only few cases of hypersensitivity reactions to aluminium such as dermatitis, either localized or systemic were described (19).

Recently, there have been data published indicating a possible link between exposure to aluminium and development of an Alzheimer's disease, however, this association still remains unproven as the estimated amount of aluminium absorbed by the body from the food is much higher than from vaccination (15).

Global Advisory Committee on Vaccine Safety (GACVS), which is a scientific advisory body of the World Health Organization in their report issued in June 2012 stated, that there are no scientific evidence of any harm related to aluminum-adjuvanted vaccines and similarly no link with autism (20 - 22). Moreover, GACVS pointed out that many incorrect assumptions on suspected associations of aluminium with neurological disease development coupled with the lack of reliable

data in ecological studies, as correlation of vaccine aluminium exposure and its outcomes on population averages, were not found or recognized as valid. Despite that, GACVS advised to continue clinical trials and epidemiological studies on monitoring and tracing evidence of aluminium safety (22).

Safety of HPV vaccination with aluminium-adjuvanted vaccine was also confirmed by GACVS statement released on 12 March 2014. After reviewing evidence on cases of macrophagic myofasciitis (MMF) – a rare muscle disease, characterized by microscopic lesions contained aluminium salts, primarily related to immunization with aluminium-adjuvanted vaccines, GACVS did not find any scientific evidence on relations of aluminium present in HPV vaccine and skin reactions occurring at the injection site (MMF) with any autoimmune syndrome (23). European Medicines Agency reviewed of registered HPV vaccines to further clarify aspects of their safety profile due to probability of occurrence of cause-effect link between administration of the vaccine against HPV and the presence of rare pain syndromes and dysfunction of the autonomic nervous system (24). The review concluded that based on evidence, there is no casual link between HPV vaccines and development of analysed syndromes ie. complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) (25).

Several studies on aluminium pharmacokinetics have also been performed. Study on *in vivo* absorption of aluminium-containing vaccine adjuvants has been performed on rabbits using the ^{26}Al isotope as a tracer. Concentrations of aluminium in blood and urine of the animals were measured during the entire experiment. Based on the results, it was estimated that administration of a dose contained 0,85 mg of aluminium to adults, results in increasing of its concentration in plasma by approx. 0,04 ng/ml (about 0,8%) (26). According to the above presented data, the hypothesis that the amount of aluminium administered to the body via vaccination contributes significantly within the general exposure of humans to aluminium seems rather unlikely (2).

Safety of vaccines used according to the immunization program was confirmed by pharmacokinetic studies conducted by the US Food and Drug Administration (FDA), where the estimated risk for infants was found extremely low (17). These results finally updated the results of previously performed studies on aluminium toxicokinetics (27) where half-life of elimination of aluminium from the body was estimated approximately as 24 hours. Recently published studies provided data on benefits of the use of aluminium-containing vaccines far outweighing any theoretical concerns about the potential negative effects of aluminium on human health.

Analysis of the Immunization Schedule in Poland on the amount of vaccines doses obligatory given during the first year of life revealed that aluminum exposure is much lower than those originating from American Immunization Schedule. According to ACIP recommendations in 2011, maximal aluminium exposure in infants from vaccination schedule over the first year of life has related to 4.225 milligrams of Al^{3+}. Adoption of the same criteria to Immunization Schedule in Poland in 2015 (28), maximal aluminium exposure in infants from vaccination schedule over the first year of life was estimated as 2.850 milligrams of Al^{3+} (see tab. I).

It should be noticed however, that 1,25 mg per human dose as maximal allowable concentration of aluminium present in a vaccine, is far above a real value. The exact concentration per human dose in most vaccines is even two-three times lower. For example according to the Summary of Product Characteristics, DTP (IBSS BIOMED S.A.), whole-cell vaccine against diphtheria, tetanus and pertussis, contains not more than 0,7 milligrams of Al^{3+} per human dose and ENGERIX B (GSK Biologicals S.A.) or Euvax B (LG Life Sciences Poland Sp z o.o.) - vaccines against hepatitis B for infants and children contain 0,25 milligrams of Al^{3+} per human dose.

Table I. Aluminium exposure in infants over the first year of life based on Immunization Schedule in Poland in 2015.

Type of vaccine	Age of administration	Aluminium content (mg) per dose
Hep B	0	0.25
Hep B	2. month	0.25
DTP	2. month	0.7
DTP	3. – 4. month	0.7
DTP	5. – 6. month	0.7
HepB	7. month	0.25

* HepB – Hepatitis B vaccine
DTP – Diphtheria, tetanus and pertussis (whole cell) vaccine (adsorbed)

CONCLUSIONS

Aluminium adjuvants are widely used in vaccines for over six decades, and its both efficiency and safety show good and established profiles. Although they show some limitations such as no Th1 reactivity and stability in temperatures below 2ºC, its easy application, safe profile and low production costs are regarded as reasonable advantages, especially in vaccines used developing countries. Further studies on aluminium-based adjuvants in relation to the immune response and stability achieved by adsorbed antigens might influence the development of their new derivatives or alternatives.

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From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 11 Jan 2018 15:45:33 +0000
To: Vaughn, William (CDC/OID/NCEZID) (CTR)
Subject: FW: Kennedy News & Views: A Lone FDA Scientist Could End the Autism Epidemic

Frank DeStefano, MD, MPH

From: World Mercury Project [mailto:(b)(6)
Sent: Wednesday, January 10, 2018 9:00 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: Kennedy News & Views: A Lone FDA Scientist Could End the Autism Epidemic

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 11 Jan 2018 15:22:59 +0000
To: Vaughn, William (CDC/OID/NCEZID) (CTR)
Cc: Shimabukuro, Tom (CDC/OID/NCEZID);McNeil, Michael (CDC/OID/NCEZID)
Subject: FW: PAM17-2171R Decision Letter

FYI – no publication date yet.
Frank DeStefano, MD, MPH

From: (b)(6)
Sent: Thursday, January 11, 2018 10:08 AM
To: (b)(6)
Cc: (b)(6) Destefano, Frank (CDC/OID/NCEZID) ; McNeil, Michael (CDC/OID/NCEZID) ; (b)(6)
Subject: Re: PAM17-2171R Decision Letter

Fantastic news! Congratulations.

(b)(6)

On Jan 10, 2018, at 5:33 PM, (b)(6) wrote:

> Dear All,
> I am please to inform you that our paper in (b)(6) has been accepted. Please see the email below.
> Thank you for all you help on this paper.
>
> (b)(6)
>
> **From:** (b)(6)
> **Sent:** Wednesday, January 10, 2018 3:35 PM
> **To** (b)(6)
> **Subject:** PAM17-2171R Decision Letter
>
>
>
> ---
>
> January 10, 2018

(b)(6)
Kaiser Permanente Northern California
Division of Research
2000 Broadway
Oakland, California CA 94612

RE: Vaccination Patterns in Children after Autism Spectrum Disorder Diagnosis and in their Younger Siblings

Dear (b)(6)

We are pleased to accept your manuscript for publication in JAMA Pediatrics. Your manuscript is accepted with the understanding that its contents, all or in part, have not been published elsewhere and will not be published elsewhere in print or electronic format without the consent of the editor. Please refer to manuscript #PAM17-2171R in any future correspondence. Also, please remember that you should not disclose the fact that your manuscript has been accepted to anyone, except coauthors and contributors and as noted below, without permission of the editor.

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Sincerely,

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From: World Mercury Project
Sent: 11 Jan 2018 02:00:13 +0000
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: Kennedy News & Views: A Lone FDA Scientist Could End the Autism Epidemic

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KENNEDY NEWS & VIEWS

A Lone FDA Scientist Could End the Autism Epidemic

By J.B. Handley, Co-Founder, Generation Rescue and Board Member, World

Mercury Project

A newly published study in the Journal of Inorganic Biochemistry causes the only science vouching for the “safety” of injected aluminum adjuvant to come under extreme criticism by heavyweight scientists.

In fact, this new study places the burden of proof for the safety of aluminum adjuvants used in vaccines so squarely on the shoulders of a lone FDA scientist—Dr. Robert J. Mitkus—that he alone could permanently change the outcome of the autism debate. Forever.

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From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 24 Jan 2018 21:35:19 +0000
To: Cano, Maria (CDC/OID/NCEZID)
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR);McNeil, Michael (CDC/OID/NCEZID)
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

This might be some kind of "spam" request – Mike got the same email.
Frank DeStefano, MD, MPH

From: Cano, Maria (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 3:48 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

FYI

From: Cano, Maria (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 3:03 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

We can only provide the information that we already have on autism in the CDC website.

As Frank noted below, he does not need to answer the question directly or provide a specific response.

From: Miller, Elaine R. (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 2:52 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Cano, Maria (CDC/OID/NCEZID) <zqg9@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Hi William,
I am forwarding this to Beth. She is covering inquiry response since I am not in the office today.
Thanks,
Elaine

From: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Date: January 24, 2018 at 2:09:26 PM EST
To: Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>, Sharan, Martha (CDC/OID/NCEZID) (CTR) <liu4@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

Hey there – Elaine, I think Frank accidentally forwarded this to the wrong "miller." This is a bit unusual in that it's an invitation to comment on this guy's website (https://www.thinkable.org/users/ben). Is there a precedent for this kind of thing? I don't think it's a "real" inquiry…it's more like "we're building "expert" content for our website/platform…and want you to chime in on a hot topic"

From: Vaughn, William (CDC/OID/NCEZID) (CTR)
Sent: 24 Jan 2018 17:18:16 -0500
To: Destefano, Frank (CDC/OID/NCEZID);Cano, Maria (CDC/OID/NCEZID)
Cc: McNeil, Michael (CDC/OID/NCEZID);Miller, Elaine R. (CDC/OID/NCEZID)
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

Hey there – I'll follow up with media…but I don't think these rise to the level of legitimate inquiries. If we respond, we might point to the current ISO web pages…through our inquiry email address. But I'm not sure that's even necessary here.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 4:35 PM
To: Cano, Maria (CDC/OID/NCEZID) <zqg9@cdc.gov>
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>; McNeil, Michael (CDC/OID/NCEZID) <mmm2@cdc.gov>
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

This might be some kind of "spam" request – Mike got the same email.

Frank DeStefano, MD, MPH

From: Cano, Maria (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 3:48 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: FW: Does vaccinating infants cause Autism? FactCheck Invitation..

FYI

From: Cano, Maria (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 3:03 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Cc: Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>
Subject: RE: Does vaccinating infants cause Autism? FactCheck Invitation..

We can only provide the information that we already have on autism in the CDC website.
As Frank noted below, he does not need to answer the question directly or provide a specific response.

From: Miller, Elaine R. (CDC/OID/NCEZID)
Sent: Wednesday, January 24, 2018 2:52 PM
To: Hibbs, Beth (CDC/OID/NCEZID) <bfh0@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: 25 Jan 2018 15:36:50 -0500
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

This sounds much better. Thanks.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Thursday, January 25, 2018 3:32 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

I might try to meld the two responses a bit so that we can provide a more unified CDC response:

(b)(5)

Frank DeStefano, MD, MPH

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Thursday, January 25, 2018 2:58 PM

To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: FW: Is CDC looking at autism rates in California following the increased measles vaccination rate?

NCBDDD's proposed response was kind of unsatisfying because not only did it not address his issues, it did offer an explanation as to why his issues weren't being addressed. This is a modified response that could go out via the vaccine safety email. We could then wait to see what his response is, if any. What do you think?

(b)(5)

From: Dowling, Nicole (CDC/ONDIEH/NCBDDD)
Sent: Thursday, January 25, 2018 1:21 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Tom,

I have attached below a suggested response with relevant links (that has been vetted with communications folks in NCBDDD). If you need anything additional, please let us know.

Best,
Nicole

(b)(5)

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Thursday, January 25, 2018 8:34 AM
To: Dowling, Nicole (CDC/ONDIEH/NCBDDD) <ncd5@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Nicole,

I'm just following up on this. I'm in no way trying to create work for you or anyone else, but if there are web links, references, phone numbers, other information, etc., that I could pass along to this person I think that would be sufficient. Thanks.

Tom

From: Dowling, Nicole (CDC/ONDIEH/NCBDDD)
Sent: Friday, January 19, 2018 3:00 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Cc: Nguyen, Lyn (CDC/OID/NCEZID) <ivx1@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>; Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Tom,

You are correct that California is not funded as part of our autism surveillance cooperative agreement. I have reached out to a few folks here to gather some resources and contacts and have looped our communications staff in about using the NCBDDD mailbox. I will follow back with you to let you know how this will be addressed.

Thanks,
Nicole

Nicole F. Dowling, PhD
Chief, Developmental Disabilities Branch
Division of Congenital and Developmental Disorders
National Center on Birth Defects and Developmental Disabilities
US Centers for Disease Control and Prevention
404.498.0071 (office)
404.606.1296 (mobile)
ndowling@cdc.gov

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Thursday, January 18, 2018 4:46 PM
To: Dowling, Nicole (CDC/ONDIEH/NCBDDD) <ncd5@cdc.gov>
Cc: Nguyen, Lyn (CDC/OID/NCEZID) <ivx1@cdc.gov>; Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>; Miller, Elaine R. (CDC/OID/NCEZID) <erm4@cdc.gov>
Subject: FW: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Nicole,

I spoke to Stuart Shapira about this inquiry below that came directly to Robin Ikeda and Anne Schuchat and was relayed to us. It's really more of an ASD prevalence over time issue versus a vaccine safety issue, but we will respond to this person. Stuart explained to me that he didn't think California contributes data for the ASD prevalence estimates that CDC generates and it might be best to refer this person to state or local resources in California that work on developmental disabilities. Do you have some general CDC resources we could provide and some agency/organization or even individual contacts in in the California Department of Public Health or other health agencies/research organizations in California. I want to reply by thanking this person for his inquiry and providing him some resources and contacts that are directly relevant or useful to address his question. Stuart also indicated you might have a generic NCBDDD email for public inquiries (like CDCINFO). That might be helpful too. Thanks.

Regards,

Tom

Tom Shimabukuro, MD, MPH, MBA
Captain, U.S. Public Health Service
Deputy Director
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)
1600 Clifton Road, MS D-26, Atlanta, GA 30329

Phone: 404-498-0679, Fax: 404-498-0666
Email: TShimabukuro@cdc.gov

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Wednesday, January 17, 2018 4:13 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Yes, let's find out who the autism POC would be at NCBDDD and put them in touch. Thanks.

Frank DeStefano, MD, MPH

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Wednesday, January 17, 2018 3:47 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

I spoke to Rob. CA doesn't have anything planned. He agreed that the initial wave of vaccination is likely catch-up vaccination, not increased routine vaccination, although he indicated that the law might impact routine early childhood vaccination coverage, since parents now don't have a choice. The school coverage data used in the NYT article pulled from data that just looks at coverage for required vaccines for school entry, not at up-to-date coverage with the CDC schedule. Do you want me to contact this person and let him know that NCBDDD does surveillance for ASD and so that ASD prevalence data will be available.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Wednesday, January 17, 2018 10:11 AM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Yes, we should probably check with Rob. I am surprised by this request from Robin. It is basically about autism trends data, which is under her purview in NCBDDD. As a courtesy to Robin, I agreed that we would follow-up, but that probably just reinforces behavior that we do not want to promote – i.e. coming to us instead of Birth Defects with basic autism questions.

Frank DeStefano, MD, MPH

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Tuesday, January 16, 2018 4:57 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Maybe we can discuss this tomorrow. I was thinking that a lot of the MMR vaccination might be catch-up vaccination, not routine 12-15 month 1st dose vaccination, which might complicate looking at ASD. I could check with Rob Schecter to see if they have anything planned, since it is their data.

From: Ikeda, Robin (CDC/ONDIEH/OD)
Sent: Tuesday, January 16, 2018 4:41 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Cc: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Thanks very much, know they will appreciate hearing from you.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Tuesday, January 16, 2018 4:28 PM
To: Ikeda, Robin (CDC/ONDIEH/OD) <rmi0@cdc.gov>
Cc: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Subject: RE: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Robin,
Yes, we will follow-up with them.
Frank

From: Ikeda, Robin (CDC/ONDIEH/OD)
Sent: Tuesday, January 16, 2018 1:00 PM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: FW: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Hi Frank – would you or one of your colleagues be willing to followup with (b)(6) and Professor Oster? (b)(6) is a physician from CA who has been in touch with CDC often on a variety of topics – hearing loss, radiation, etc.

Thank you very much,
Robin

From: (b)(6)
Sent: Tuesday, January 16, 2018 8:31 AM
To: Schuchat, Anne MD (CDC/OD) <acs1@cdc.gov>; Ikeda, Robin (CDC/ONDIEH/OD) <rmi0@cdc.gov>
Cc: Emily_Oster@brown.edu
Subject: Is CDC looking at autism rates in California following the increased measles vaccination rate?

Dr. Schuchat, Dr. Ikeda:

I read with interest Prof. Oster's Op-Ed piece in today's NY Times and asked her if she or anyone else was looking at autism rates in California following the successful increase of measles vaccination after the 2014 Disneyland

outbreak.https://www.nytimes.com/2018/01/16/upshot/measles-vaccination-california-students.html?action=click&contentCollection=Fashion & Style&module=Trending&version=Full®ion=Marginalia&pgtype=article

As I was typing my email to her, I thought, "Why not go to the source?" I think this falls within Dr. Schuchat's purview, but am including Dr. Ikeda just in case it's in the other half of CDC.

I like "experiments of nature" where an action taken for one purpose can provide insight into something else. As you know, I am a semi-retired internist/geriatrician with little knowledge of childhood vaccines, but I hope someone at CDC is looking or will look at the autism rates in California for the years beginning in 2014 and perhaps for a decade.

When the president and many others still think that childhood vaccines cause autism Donald Trump Has Long Linked Autism to Vaccines. He Isn't - Fortune andTrump's Dangerous Support for Conspiracies About Autism and …, it's important to answer the question "Do vaccines cause autism?" for once and for all. The increased vaccination rates in California provide an ideal opportunity to answer the question. The recent report in JAMA indicating a stabilization of the incidence of autism spectrum Frequency of Autism Spectrum Disorder in US Stable in Recent Years didn't provide detailed enough information to address this question. Obviously, if the MMR vaccine causes autism (I assume the children being vaccinated are receiving MMR- I don't even know if there is a separate measles vaccine and if there is, whether pediatricians stock it in their offices) there should be a big increase in cases of autism reported, especially in those school districts where the vaccination rate went from very low to very high.

I am copying Prof. Oster on this email so she is aware and in case someone from CDC wants to contact her.

Thanks in advance for anything you can do on this topic, and as always thanks for all you do to protect the health of the American public.

Sincerely,

(b)(6)

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: 23 Jan 2018 14:24:15 -0500
To: Sharan, Martha (CDC/OID/NCEZID) (CTR)
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR);Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Media Request - Time Sensitive

I think most flu vaccine is thimerosal free or has trace thimerosal, which means it was used in the manufacturing process and them removed and is at undetectable levels. However, the Vaccine Supply and Assurance Branch in ISD/NCIRD would be the experts or even the manufacturers themselves.

From: Sharan, Martha (CDC/OID/NCEZID) (CTR)
Sent: Tuesday, January 23, 2018 2:06 PM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>; Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: RE: Media Request - Time Sensitive

Tom:
One follow- up question from the reporter on this:

> Is thimerosal-free flu vaccine still available in limited supply per the FDA website?
>
> https://www.fda.gov/biologicsbloodvaccines/vaccines/questionsaboutvaccines/ucm070430.htm
>
> "Thimerosal-preservative free influenza vaccine licensed for use in children six to 59 months of age is available in limited supply"

Martha Sharan
Media Relations Specialist/Chenega Corporation
CDC/Division of Healthcare Quality Promotion (DHQP)
404-639-2683/msharan@cdc.gov
Telework: Wed. & Fri.

From: Sharan, Martha (CDC/OID/NCEZID) (CTR)
Sent: Tuesday, January 23, 2018 11:12 AM
To: Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>; Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Subject: RE: Media Request - Time Sensitive

I agree. I'll let NMB respond with those links.
Thanks,
Martha

Martha Sharan
Media Relations Specialist/Chenega Corporation

CDC/Division of Healthcare Quality Promotion (DHQP)
404-639-2683/msharan@cdc.gov
Telework: Wed. & Fri.

From: Shimabukuro, Tom (CDC/OID/NCEZID)
Sent: Tuesday, January 23, 2018 11:09 AM
To: Sharan, Martha (CDC/OID/NCEZID) (CTR) <liu4@cdc.gov>; Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Subject: RE: Media Request - Time Sensitive

I suggest we forward the link to the CDC website and to the IOM report (http://www.nationalacademies.org/hmd/reports/2004/immunization-safety-review-vaccines-and-autism.aspx) and say we don't have anything to add.

From: Sharan, Martha (CDC/OID/NCEZID) (CTR)
Sent: Tuesday, January 23, 2018 11:03 AM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>; Shimabukuro, Tom (CDC/OID/NCEZID) <ayv6@cdc.gov>
Cc: Vaughn, William (CDC/OID/NCEZID) (CTR) <hbv2@cdc.gov>
Subject: Media Request - Time Sensitive

Frank and Tom:
News Media Branch passing along this media request. You are not obligated to respond. I'm happy to forward information that is on our web:
https://www.cdc.gov/vaccinesafety/concerns/thimerosal/index.html.
If you have anything else you would like me to include, please let me know,
Martha

Martha Sharan
Media Relations Specialist/Chenega Corporation
CDC/Division of Healthcare Quality Promotion (DHQP)
404-639-2683/msharan@cdc.gov
Telework: Wed. & Fri.

Hello,

I'm a fact check reporter with The Daily Caller News Foundation.

I am writing about a viral Facebook video (7.8M views) that says "autism is caused by mercury in vaccines."

Is there an expert available who I could speak with about this topic?

I am on deadline, so I appreciate your prompt reply!

From: Journal of Trace Elements in Medicine and Biology
Sent: 15 Jan 2018 05:23:59 +0000
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: Re: Please respond to invitation to review for Journal of Trace Elements in Medicine and Biology [180112-008395]

How was our service today?

Dear Dr. DeStefano,
Upon checking I see that you are yet to respond to the invitation.
Also, I see that you have been invited in an unregistered account fxd1@cdc.gov.
Could you please let me know your registered account? If not please use the following link to register and access the submission.
https://www.evise.com/profile/#/JTEMB/login
Please let me know if there is anything else I can help you with.
Regards,
(b)(6)

Ascendas International Tech Park (Crest, 12th Floor), Taramani road, Taramani, Chennai 600 113

From: Frank (CDC/OID/NCEZID) Destefano
Date: 12/01/2018 03.13 PM

***** External email: use caution *****

I just accepted. I tried last week but the website seemed to have been down.

Frank DeStefano, MD, MPH

From: Journal of Trace Elements in Medicine and Biology [mailto:(b)(6)
Sent: Friday, January 12, 2018 9:46 AM
To: Destefano, Frank (CDC/OID/NCEZID) <fxd1@cdc.gov>
Subject: Please respond to invitation to review for Journal of Trace Elements in Medicine and Biology

This message was sent automatically. Please do not reply.

Ref: JTEMB_2018_2
Title: Aluminium in brain tissue in autism- Some essential considerations
Journal: Journal of Trace Elements in Medicine and Biology

Corresponding Author: Corresponding Author: Bahadur Singh
Co-authors: Co-authors: Kewal Krishan, Tanuj Kanchan

Dear Dr. DeStefano,

I recently invited you to review the above-referenced manuscript. This is a friendly reminder asking for a response to my invitation. As you are an acknowledged expert in this field, I would greatly appreciate your contribution.

Please find the abstract of the manuscript at the end of this message.

If you have any concerns about potential conflicts of interest, please consult the Editor.

If you are willing to review this manuscript, please click on the link below to navigate:

Register to accept

If you accept this invitation, I would appreciate your submitting your review within 14 days.

Please submit your review via EVISE® at:
http://www.evise.com/evise/faces/pages/navigation/NavController.jspx?JRNL_ACR=JTEMB.

If you cannot review this manuscript, please click on the link below. I would also appreciate your suggestions for alternate reviewers.

Decline

I look forward to receiving your response.

Kind regards,

(b)(6)

Journal of Trace Elements in Medicine and Biology

Abstract:

Autism spectrum disorders (ASD) are the set of behavioral traits, associated with individuals with impaired social communication, which may inhibit the individual for his/her social inclusion. The underlying mechanism of the development of ASD is yet to fully understand. A recent publication (M. Mold, D. Umar, A. King, C. Exley, Aluminium in brain tissue in autism, J. Trace Elem. Med. Biol. 2017) presenting the association of Aluminium in the brain cells with autism of five individuals diagnosed with ASD raised concerns over the research design and cognitive bias. This correspondence highlights the research design, cognitive bias and some ethical issues related to the paper.

institute. Just click on 'Go to Review' and then on the 'Go to Scopus' link under the Useful links section on the My Review tab or click here for more information.

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