Increasing Exposure to Antibody-Stimulating Proteins and Polysaccharides in Vaccines Is Not Associated with Risk of Autism

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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;■:■-■).*

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

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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

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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

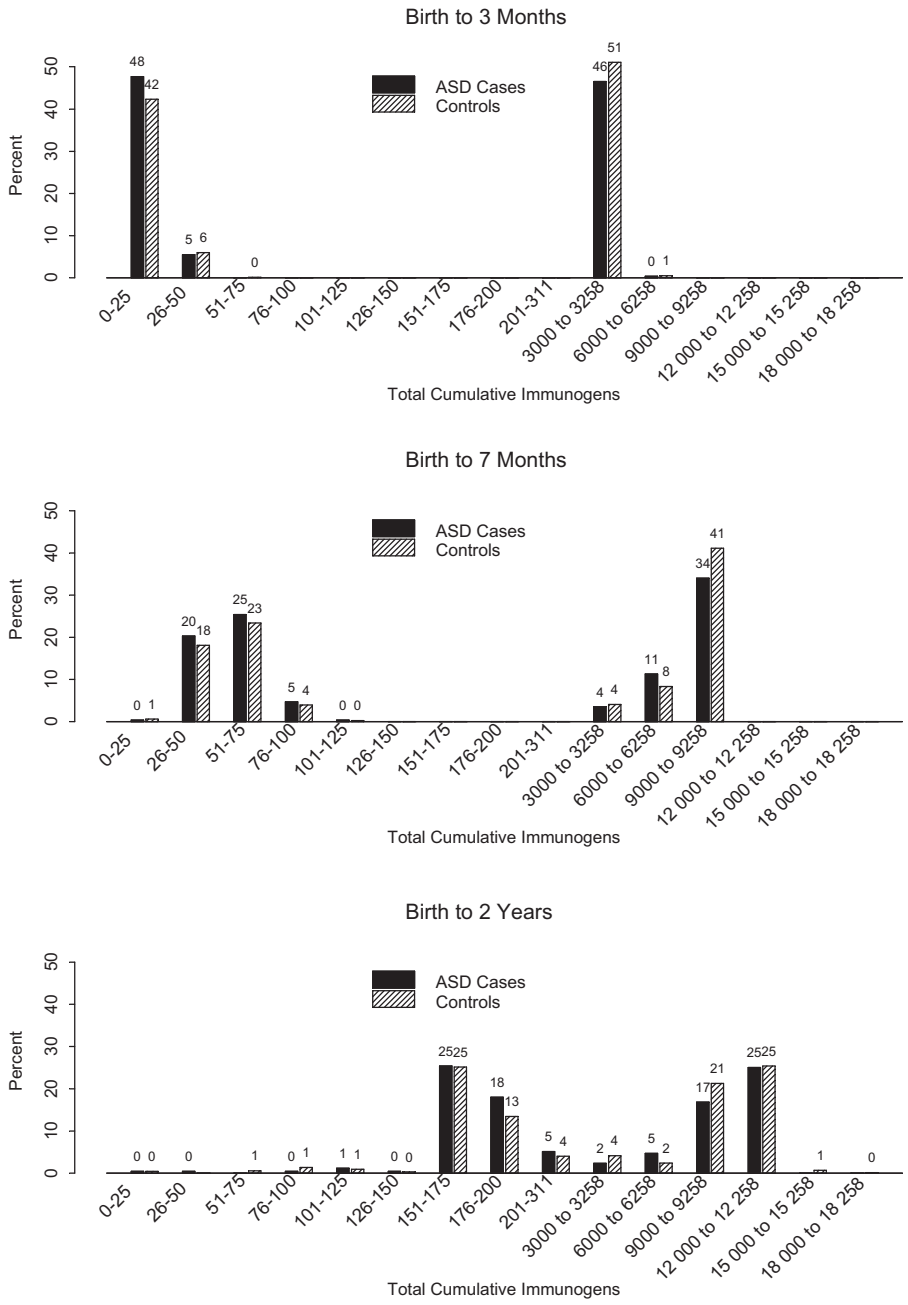

Figure 1. Distribution of total cumulative antigen exposure among ASD cases and controls, by age range.

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

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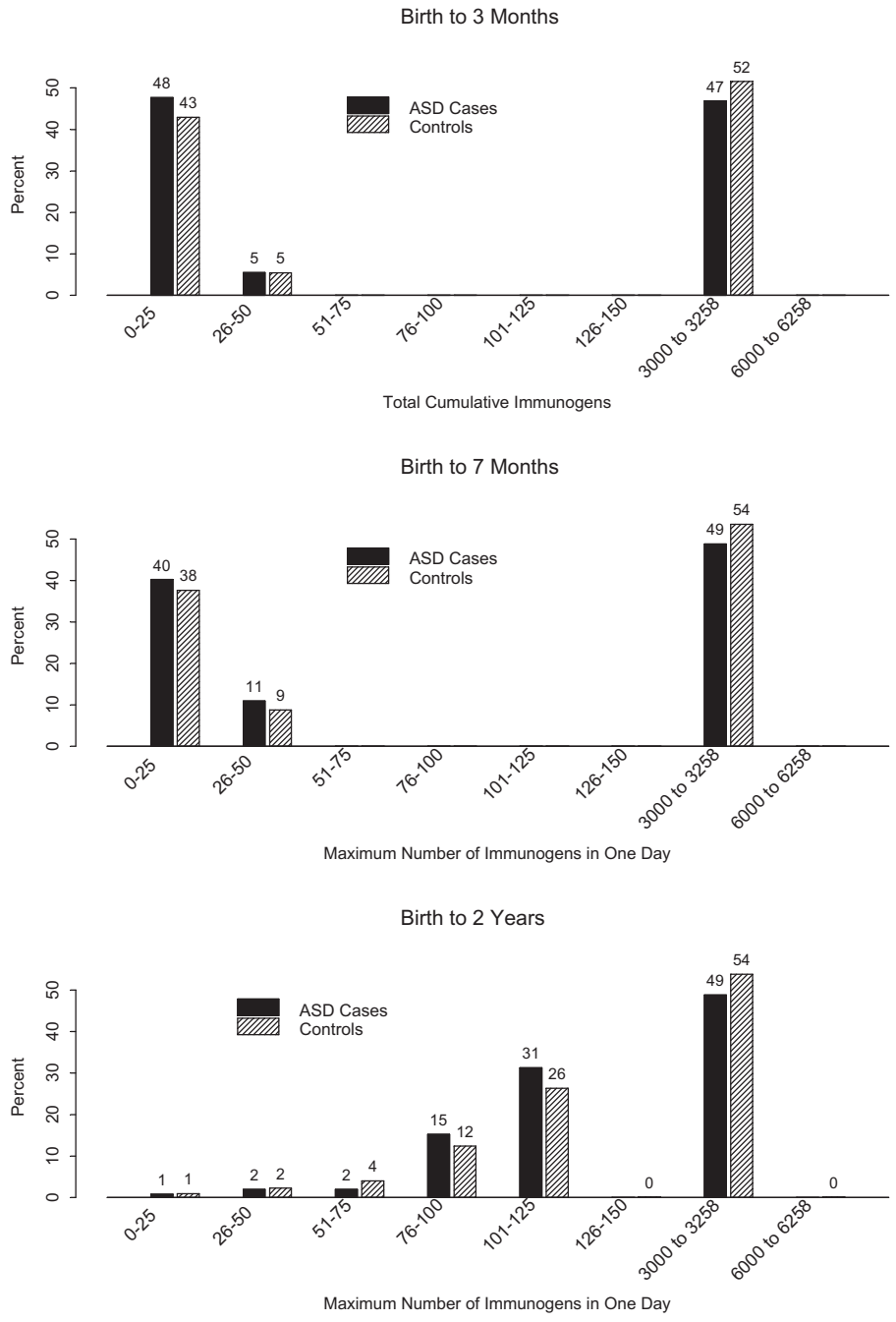

Figure 2. Distribution of maximum antigen exposure in a single day among ASD cases and controls, by age range.

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. ■

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