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Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta

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ABSTRACT. *Objective.* **To compare ages at first measles-mumps-rubella (MMR) vaccination between children with autism and children who did not have autism in the total population and in selected subgroups, including children with regression in development.**

Methods. **A case-control study was conducted in metropolitan Atlanta. Case children ($N = 624$) were identified from multiple sources and matched to control children ($N = 1824$) on age, gender, and school. Vaccination data were abstracted from immunization forms required for school entry. Records of children who were born in Georgia were linked to Georgia birth certificates for information on maternal and birth factors. Conditional logistic regression was used to estimate odds ratios (ORs).**

Results. **The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children; most case (70.5%) and control children (67.5%) were vaccinated between 12 and 17 months of age. Similar proportions of case and control children had been vaccinated before 18 or before 24 months. No significant associations for either of these age cutoffs were found for specific case subgroups, including those with evidence of developmental regression. More case (93.4%) than control children (90.6%) were vaccinated before 36 months (OR: 1.49; 95% confidence interval: 1.04–2.14 in the total sample; OR: 1.23; 95% confidence interval: 0.64–2.36 in the birth certificate sample). This association was strongest in the 3- to 5-year age group.**

Conclusions. **Similar proportions of case and control children were vaccinated by the recommended age or shortly after (ie, before 18 months) and before the age by which atypical development is usually recognized in children with autism (ie, 24 months). Vaccination before 36 months was more common among case children than control children, especially among children 3 to 5 years of age, likely reflecting immunization requirements for enrollment in early intervention programs.** ***Pediatrics*** **2004; 113:259–266;** ***autism, autism spectrum disorders, MMR vaccine, immunizations, epidemiology.***

ABBREVIATIONS. MMR, measles-mumps-rubella; IOM, Institute of Medicine; MADDSP, Metropolitan Atlanta Developmental Disabilities Program; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*; ASD, autism spectrum disorder; MR, mental retardation; OR, odds ratio; CI, confidence interval.

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Autism is a serious, life-long developmental disorder characterized by marked impairments in social interactions; communication skills; and repetitive, restrictive, or stereotyped behaviors, interests, and activities.[1] Recent studies have suggested that the prevalence of autism is higher (30–60 per 10 000 children)[2–5] than in studies conducted 15 to 20 years ago (4–5 per 10 000).[6–10] The apparent increase in prevalence, coupled with reports of increasing numbers of children with autism being served by schools and service agencies,[11–14] has prompted concerns that environmental exposures might be causing autism. Vaccines, particularly the measles-mumps-rubella (MMR) vaccine, are among the exposures for which there has been a great deal of speculation of a possible association with autism.

Wakefield et al[15] were the first to propose that MMR vaccine might be causally linked to autism. They published a report describing 12 pediatric patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism. In 8 of the 12 cases, the children's parents or pediatricians suggested that MMR vaccine might have contributed to the onset of behavioral problems. The same investigators subsequently proposed a new syndrome consisting of certain gastrointestinal conditions associated with behavioral regression[16] and reported identifying laboratory evidence of measles virus genome in the peripheral white blood cells and bowel biopsy specimens of a few such patients. The investigators, however, did not distinguish whether the virus was wild measles virus or vaccine strain virus.[17,18] Several epidemiologic studies have not found an association between MMR vaccination and autism.[19–24] The Institute of Medicine (IOM)[25] reviewed the MMR-autism hypothesis and rejected a causal association at the population level but encouraged additional studies to evaluate more fully the possibility that there are subgroups of children who might be at increased risk of autism from MMR vaccination.

To examine further a possible relationship between MMR vaccine and autism, including in different subgroups of children, we conducted a large

case-control study in metropolitan Atlanta in which we compared the MMR vaccination histories of a population-based sample of children with autism and school-matched control children who did not have autism.

METHODS

Study Population

Children with autism were identified from the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP), a multiple-source, population-based surveillance program that monitors the occurrence of selected developmental disabilities among children in the 5-county metropolitan Atlanta area.[5,26] In 1996, the first year in which autism was included, MADDSP identified 987 children 3 to 10 years of age with autism, for a prevalence of 3.4 per 1000 children.[5] The autism cases were identified through screening and abstraction of source files at schools, hospitals, clinics, and specialty providers. Clinical psychologists with expertise in the diagnosis of autism reviewed the abstracted records according to a standardized coding scheme to determine the presence of behavioral characteristics consistent with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV)[1] criteria for autism spectrum disorders (ASDs). The study was approved by the Centers for Disease Control and Prevention's institutional review board. Because the activity was considered public health surveillance, parental consent was not required. Instead, permission to access records was obtained from each data source.

For the current study, case children were derived from the 987 children who were originally identified in the 1996 MADDSP prevalence year. During the period from 1999 through 2001, we were able to locate school records with the required immunization documents for 660 case children. We were not able to find school immunization records for the remaining children because the children had moved out of state, transferred to a school in a county that was not under MADDSP's jurisdiction, transferred to a private school that was not accessible by MADDSP, or were being home schooled. When a child moved or transferred, the child's permanent school record, including immunization form, was transferred to the child's new school. We were not able to quantify how many children were lost for each of these reasons because of incomplete record keeping at the schools. An additional 17 case children were excluded from the study because we could not identify matched control children for them.

We attempted to match 3 control children to each case child and were successful for 97% of the case children; the remaining case children had fewer matched control children. Control children were selected from regular education programs and were matched to case children based on age in 1996 (within 1 year), gender, and school of attendance at the time of abstraction. However, when a case child was attending a psychoeducational school, a special school for children with behavioral and developmental difficulties, control children were selected from the school in the child's residential area that the child would have attended had the child not had a disability. In addition, when a case child was in the last elementary grade level before middle school and was older than other children in his or her grade level, control children were selected from the middle school that the case child normally would have attended.

We excluded case and control children from the study when they were missing a vaccination form (15 case children and 14 control children). We also excluded children with incomplete vaccination forms when the form did not list at least 1 diphtheria-tetanus-pertussis vaccine by 2 years of age or at least 1 MMR vaccination at any age (4 case children and 1 control child). Children with a religious or medical exemption (1 case and 1 control) were not excluded from the study. After all exclusions, 624 case and 1824 control children remained in the study.

Classification of Autism Subgroups

The MADDSP data files were reviewed by a developmental pediatrician (M.Y.A.) to identify subgroups of children with potentially different susceptibilities to development of autism from an environmental exposure, such as MMR vaccine. These groups, which were not mutually exclusive, included 1) children without any indication of developmental delay before 12 months of age (ie, before the recommended age of the first MMR vaccination) or a preexisting condition, 2) children with any indication of loss of age-appropriate developmental skills (regression) or appropriate skills that failed to progress (plateau), and 3) children with and children without coexisting mental retardation (MR). Children without any indication of developmental delay at <1 year of age were children who did not lack any speech at appropriate ages, including cooing and babbling, and were socially responsive in the first year of life (eg, cuddling, appropriate eye contact, responding to parents voices). Children without a preexisting condition included children who did not have a major birth defect, a co-occurring developmental disability, or a major perinatal or postnatal insult (eg, infection, injury) that could have contributed to developmental delays. Children without a preexisting condition and without evidence of delay before 1 year of age were grouped into a single category. MR was defined as an IQ of 70 or less on the most recent psychometric test. We also attempted to examine information on family history of autism spectrum conditions or other developmental disabilities, but this information was incomplete in the records and not useful for analysis.

Vaccination History

Trained abstractors collected vaccination histories for both case and control children from the standardized state immunization forms that are required for all children who attend school and early intervention programs in Georgia. The forms are placed in each student's permanent school file that is kept at the school where the child is enrolled. During the period in which children in our study would have enrolled in school, Georgia law required at least 1 dose of measles, mumps, and rubella vaccines, usually administered at 15 months of age as the combined MMR vaccine. Vaccination was also required for enrollment in preschool special education programs for 3- to 5-year-old children with disabilities.

Other Data Collection

For children with autism, additional developmental disability–related information was obtained from MADDSP data files. This included information on the presence of other developmental disabilities, epilepsy, and IQ level (for categorization of MR). In addition, we identified major birth defects among the case children by matching with Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program, a population-based surveillance program of major birth defects that covers the same geographic area.[27]

For all case and control children, we obtained demographic information, including date of birth, gender, race, and birth state, from the birth certificate or registration form that is kept in each child's permanent school record. We matched 355 (56%) case and 1020 (56%) control children to Georgia state birth certificate records, which allowed us to obtain additional information, such as each child's birth weight and gestational age and the mother's parity, age, race, and education.

Statistical Analyses

Determining exposure–disease associations requires knowledge of dates of exposure and onset of illness. Autism, however, usually does not have a well-demarcated date of onset. Other studies have tried to address the possible relationship to MMR vaccination by examining the temporal relationship between vaccination and onset of initial parental concern, date of first diagnosis of autism, or onset of regression (if present). We had incomplete information on these events, so we compared the distribution of ages at first MMR vaccination between case and control children. The assumption implicit in this exposure comparison is that if the MMR vaccine increases the risk of autism, which usually develops before 24 months of age, then children who are vaccinated at younger ages would have a higher risk of developing autism. The age at exposure was examined in a number of ways. First, we compared the overall distributions of age at vaccination. We then analyzed associations using 3 specific age cutoffs: 1) <18 months of age, as an indicator of "on-time" vaccination according to the recommended vaccination schedule for MMR vaccine[28]; 2) <24 months of age, the age by which atypical development has become apparent in most children with autism[23,29–32]; and 3) <36 months of age, the age by which autistic characteristics must have developed to meet DSM-IV criteria for autism.[1]

We used the χ^2 statistic for categorical comparisons of the

characteristics of case and control children. We compared the overall distributions of ages at first MMR vaccination using a likelihood ratio test in a conditional logistic regression model stratified by matched sets in which age at vaccination was included as a categorical variable with 5 age categories. We also used conditional logistic regression models to estimate the odds ratios (ORs) for the association between autism and age at MMR vaccination dichotomized according to the 3 prespecified age cutoffs (18 months, 24 months, and 36 months).

In the subgroup of children that we matched to birth certificate files, we were able to adjust for additional factors. Potential confounding variables were evaluated individually for their association with autism case status. Those with a $P < .20$ were included as covariables in conditional logistic regression models to estimate adjusted ORs.[33] In analyses stratified by birth or maternal characteristics, we were not able to maintain the matched sets in the analysis. However, we did include the matching factors (age, gender, and school) as covariables in the regression models.

RESULTS

Case Selection

The 624 case children included in the analysis and the 363 excluded case children were similar with respect to age and gender (Table 1). Although a somewhat larger proportion of included (60%) than excluded (56%) case children had evidence of MR, this difference was not statistically significant.

Clinical Features of Autism Cases

Among the 624 case children, 378 had MR, 31 had cerebral palsy, 8 had visual impairment, 7 had hearing loss, 49 had epilepsy, and 31 had congenital malformations. A total of 234 cases were identified with at least 1 preexisting condition (eg, congenital malformation, metabolic disorder, fetal alcohol syndrome, intraventricular hemorrhage) or indications of developmental delay before 1 year of age. On the basis of record review, we identified 80 case children with evidence of regression or plateau in developmental milestones after 12 months of age

Demographic Characteristics of Case Children and Matched Control Children

In the total sample, case and control children were matched appropriately on age and gender, with a preponderance of boys in both groups (Table 2). The racial distributions were also fairly similar, although a larger proportion of control (10%) than case (6%) children were classified as "other" race and both groups had an appreciable number for which race information was missing.

TABLE 1. Comparison of Demographic Characteristics and Cognitive Levels Between Included and Excluded Autism Case Children

Characteristic	Included Cases ($N = 624$)		Excluded Cases ($N = 363$)	
	n	%	*n*	%
Age group (y)				
3–5	214	34	131	36
6–10	410	66	232	64
Gender				
Male	500	80	292	80
Female	124	20	71	20
Mental retardation				
Yes	376	60	205	56
No	248	40	158	44

The similarities in age and gender were also observed in the 355 case and 1020 control children who were matched to the Georgia birth certificate files (Table 2). In this subsample, the racial distributions of case and control children were the same and no children had missing race data. Using data that were available only in the birth certificate files, we did find several differences between case and control children. Compared with control children, case children were significantly ($P < .05$) more likely to have had a low birth weight and to have been the product of a multiple-birth pregnancy. At the time of delivery, mothers of case children tended to be older and to have had higher levels of education.

Comparisons of Ages at MMR Vaccination

The overall distributions of ages at first MMR vaccination were similar ($P = .22$) for case and control children (Fig 1). Most case (70.5%) and control (67.5%) children were vaccinated between 12 and 17 months of age.

When we performed the analyses dichotomizing age at vaccination, we found that vaccination before 18 months or 24 months of age was not associated with case status, either overall or in the different gender or age subgroups (Table 3). Using a 36-month cutoff, more case children (93%) than control children (91%) were vaccinated before 36 months of age (OR: 1.49; 95% confidence interval [CI]: 1.04–2.14); the association was strongest in children 3-to-5 years of age (OR: 2.34; 95% CI: 0.99–5.54). Although the OR was higher among boys than among girls, the gender-specific ORs were not significantly different (likelihood ratio test *P*-value = 0.27 for the interaction of gender and age at vaccination <36 months).

In the analyses using the birth certificate subsample, we were able to adjust for potential confounding variables. All of the ORs were lower than those in the total sample, except those for the 3- to 5-year age group vaccinated before 24 months or before 36 months (Table 3). However, because of the smaller size of the birth certificate sample, the 95% CIs for all age categories were wider and included 1.0. Although the birth certificate sample results in Table 3 were adjusted for maternal and birth characteristics, the ORs were not different from unadjusted results for the birth certificate sample (data not shown), indicating that there was little to no confounding effect by these factors.

Results for Subgroups of Case Children

When we performed analyses within the nonmutually exclusive clinical subgroups of case children, we found no associations with vaccination before 18 months or 24 months of age among cases without preexisting conditions before 1 year of age, case children with regression or plateau, and case children with and without MR (Table 4). Using a 36-month age cutoff, the ORs in all subgroups of case children were above 1.0, but only the OR among case children without MR had a CI that excluded 1.0. None of the adjusted results using the birth certificate sample was statistically significant. In the birth certificate sample, however, only 3 case children without men-

TABLE 2. Characteristics of Cases and Control Subjects in the Total Sample and the Birth Certificate Sample

Variable Category	Total Sample				Birth Certificate Sample			
	Controls		Cases		Controls		Cases	
	n	%	*n*	%	*n*	%	*n*	%
Age (y) in 1996								
3–5	623	34	214	34	376	37	127	36
6–10	1201	66	410	66	644	63	228	64
Gender								
Male	1462	80	500	80	809	79	282	79
Female	362	20	124	20	211	21	73	21
Race								
White	918	50	333	53	571	56	199	56
Black	636	35	230	37	384	38	137	39
Other	174	10	40	6	65	6	19	5
Missing	96	5	21	3	0	0	0	0
Maternal age (y)								
<20					95	9	15	4
20–34					803	79	280	79
35+					122	12	60	17
Maternal education (y)								
≤12					466	46	135	38
13–15					253	25	100	28
16+					301	30	120	34
Birth weight (g)								
0–1499					11	1	12	3
1500–2499					52	5	37	10
2500+					957	94	306	86
Multiplicity								
Singleton					990	97	329	93
Twin+					30	3	26	7
Parity								
First born					452	44	149	42
Second or higher					560	55	204	57
Missing					8	1	2	1
Total	1824	100	624	100	1020	100	355	100

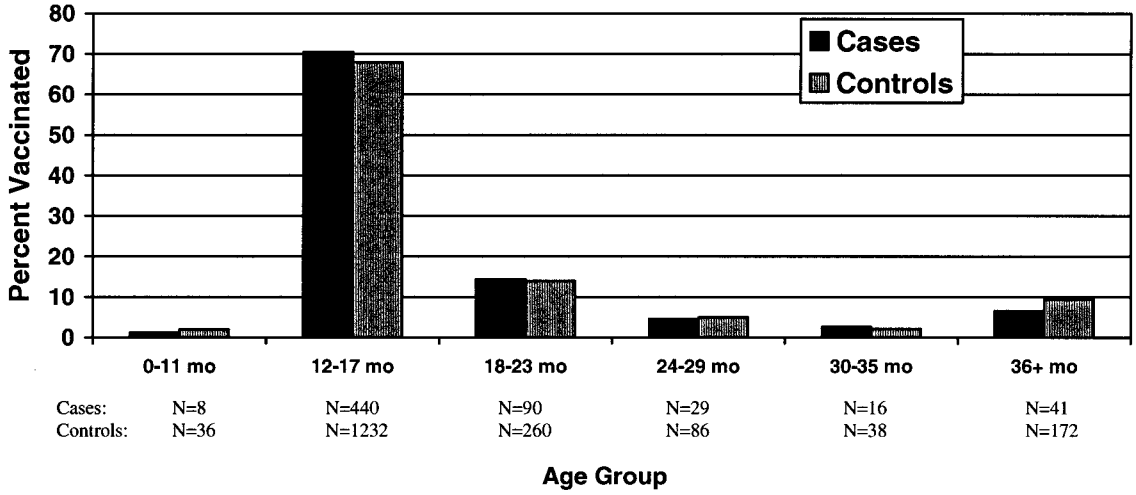

Fig 1. Age at first MMR vaccination by case status for total sample.

tal retardation were vaccinated after 36 months of age, resulting in a highly unstable OR estimate for this subgroup.

Results According to Race, Birth Weight, and Maternal Characteristics

We further examined associations according to selected maternal and birth characteristics that were available from the birth certificate files. For vaccination before 18 months or 24 months of age, all of the ORs according to different categories of race, birth weight, maternal age, and maternal education were <1.0 (Table 5). For the 36-month cutoff, there were suggestions of possible associations within the subgroups of children whose mothers were older or had more years of education, but the CIs were very wide and included 1.0.

DISCUSSION

In this population-based study in a large US metropolitan area, we found that the overall distribution of ages at first MMR vaccination among children

TABLE 3. Association Between Age at First MMR Vaccination and Autism Case Status for the Total Sample and the Birth Certificate Sample and According to Gender and Age

Sample	Case Subgroup	Cases	<18 Months, OR (95% CI)	<24 Months, OR (95% CI)	<36 Months, OR (95% CI)
Total sample	All cases	624	1.12 (0.91–1.38)	1.21 (0.93–1.57)	1.49 (1.04–2.14)
Unadjusted analyses*	Boys	500	1.22 (0.97–1.54)	1.29 (0.96–1.73)	1.67 (1.10–2.53)
	Girls	124	0.83 (0.52–1.30)	0.96 (0.55–1.68)	1.06 (0.51–2.20)
	Aged 3–5 y	214	1.08 (0.73–1.60)	1.66 (0.95–2.92)	2.34 (0.99–5.54)
	Aged 6–10 y	410	1.14 (0.90–1.46)	1.10 (0.82–1.49)	1.33 (0.89–1.98)
Birth certificate sample	All cases	311	0.93 (0.66–1.30)	0.99 (0.63–1.55)	1.23 (0.64–2.36)
Adjusted analyses†	Boys	243	0.94 (0.65–1.38)	1.01 (0.61–1.67)	1.64 (0.77–3.49)
	Girls	68	0.79 (0.33–1.86)	0.84 (0.26–2.77)	0.24 (0.04–1.47)
	Aged 3–5 y	112	0.77 (0.39–1.50)	1.67 (0.60–4.67)	2.63 (0.51–13.45)
	Aged 6–10 y	199	0.98 (0.65–1.47)	0.87 (0.51–1.46)	1.09 (0.52–2.30)

* Conditional logistic regression model stratified by the matching variables (age, gender, school).
† Conditional logistic regression model stratified by the matching variables (age, gender, school) and adjusted for birth weight, multiple gestation, maternal age, and maternal education. The number of cases ($N = 311$) is less than the number of cases with birth certificate data because some cases had no matched controls with birth certificate data.

TABLE 4. Associations Between Age at First MMR Vaccination and Autism Case Status Within Selected Clinical Subgroups of Cases for the Total Sample and the Birth Certificate Sample

Sample	Case Subgroup	Cases	<18 Months, OR (95% CI)	<24 Months, OR (95% CI)	<36 Months, OR (95% CI)
Total sample	No preexisting conditions <1 y‡	390	1.07 (0.83–1.39)	1.14 (0.82–1.59)	1.51 (0.96–2.37)
Unadjusted analyses*	Regression or plateau	80	1.37 (0.78–2.41)	1.30 (0.64–2.66)	1.45 (0.54–3.93)
	With MR§	376	1.06 (0.82–1.38)	1.09 (0.79–1.51)	1.21 (0.79–1.84)
	Without MR	248	1.23 (0.87–1.73)	1.46 (0.93–2.30)	2.45 (1.20–5.00)
Birth certificate sample	No Preexisting Conditions <1 y‡	187	1.05 (0.68–1.61)	1.02 (0.56–1.86)	1.82 (0.77–4.31)
Adjusted analyses†	Regression or Plateau	31	0.83 (0.23–3.09)	0.41 (0.07–2.29)	0.69 (0.14–3.30)
	With MR§	179	1.13 (0.72–1.79)	0.96 (0.54–1.71)	0.82 (0.38–1.79)
	Without MR	132	0.68 (0.40–1.16)	1.02 (0.47–2.22)	3.55 (0.74–17.07)

* Conditional logistic regression model stratified by the matching variables (age, gender, school).
† Conditional logistic regression model stratified by the matching variables (age, gender, school) and adjusted for birth weight, multiple gestation, maternal age, and maternal education.
‡ Includes children without any indication of developmental delay at <12 months, a major defect, co-occurring developmental disability, or a major perinatal or postnatal insult.
§ Defined as an IQ of ≤70 on the most recent psychometric test.

TABLE 5. Associations Between Age at First MMR Vaccination and Autism Case Status According to Race, Birth Weight, and Maternal Characteristics in the Birth Certificate Sample

Characteristic	Category	Cases	<18 Months, OR* (95% CI)	<24 Months, OR* (95% CI)	<36 Months, OR* (95% CI)
Race	White/other	218	0.87 (0.59–1.27)	0.77 (0.44–1.35)	0.89 (0.40–1.95)
	Black	137	0.83 (0.54–1.27)	0.98 (0.58–1.66)	1.68 (0.82–3.47)
Maternal age	<35 y	295	0.90 (0.67–1.22)	0.91 (0.61–1.35)	1.23 (0.71–2.11)
	35+ y	60	0.53 (0.24–1.17)	0.59 (0.16–2.23)	2.64 (0.22–31.72)
Maternal education	<16 y	235	0.94 (0.68–1.30)	0.94 (0.62–1.41)	1.18 (0.67–2.07)
	16+ y	120	0.60 (0.33–1.09)	0.61 (0.21–1.74)	2.76 (0.48–15.87)
Birth weight	<2500 g	49	0.50 (0.20–1.25)	0.48 (0.15–1.55)	1.41 (0.29–6.86)
	≥2500 g	306	0.91 (0.67–1.23)	0.93 (0.62–1.39)	1.26 (0.71–2.24)

* OR (95% CI) from unconditional logistic regression model adjusted for age, gender, school, and all factors listed in table.

with autism was similar to that of school-matched control children who did not have autism. Our hypothesis was that earlier age at vaccination, ie, before a possible critical time window for autism development, might be associated with an increased risk for autism. When we analyzed associations according to different age cutoffs, we found that similar proportions of case and control children had been vaccinated before 18 months or before 24 months of age. No significant associations for either of these age cutoffs were found for specific subgroups of case children, including children with some indication of regression or plateau in development, the group of most concern based on the clinical reports of Wakefield et al.[15] Vaccination before 36 months of age was more common among case children than control children, although only a small proportion of children in either group received their first MMR vaccination after 36 months of age.

We compared the distribution of ages at vaccination between case and control children because we lacked an unvaccinated comparison group and we had incomplete information for determining date of onset of autism. Determining onset of autism, however, is difficult even under the best of circumstances. In most instances, brain abnormalities associated with autism probably occur prenatally,[34–36] but parents might not become aware of their chil-

dren's problems until later in life, when communication delays and characteristic behaviors become apparent. Analyses of videotapes made of children before ASD diagnosis indicate that identifying onset of developmental problems is very difficult, especially retrospectively,[37,38] and that children who were reported as losing skills often had abnormal behaviors before the time when the loss was first noted.[32,39]

The US vaccination schedule recommends that the first dose of MMR vaccine be administered between 12 and 15 months of age.[28] Thus, our results for vaccination before 18 months of age evaluated possible increased risks of autism associated with vaccination by or shortly after the recommended age. Parental concerns about development or the first indications of atypical development usually occur before 24 months of age in children with autism,[23,30–32,40] and developmental regression, if it occurs, usually is noted between 12 and 24 months of age.[23,41–43] In Wakefield's case series, 10 of the 12 children had ASD and 9 (90%) of the ASD cases had atypical behaviors noted by 21 months of age.[15] Thus, we would expect that exposures that could be causally associated with autism would most likely occur before 24 months of age.

To meet DSM-IV criteria for autism, some manifestation of atypical development must be apparent before 36 months of age.[1] Of the 41 case children who were vaccinated after 36 months of age in our study, 32 (78%) had documented delays in development before 36 months of age. Rather than representing causal relationships, associations with the 36-month cutoff would be more likely than associations with earlier age cutoffs to have been influenced by factors related to the evaluation, management, and treatment of the child. For example, case children might have been more likely than control children to have been vaccinated as a requirement for enrollment in early intervention or preschool special education programs. This possibility is supported by the finding that the difference between case and control children in the proportion vaccinated before 36 months of age was strongest in the 3- to 5-year-old age group. In 1991, the Individuals with Disabilities Education Act[11] mandated the provision of special education programs for children with autism beginning at approximately 36 months of age. Thus, the case children who were 3 to 5 years of age in 1996 would have been most affected by the Individuals with Disabilities Education Act special education requirement and 98% of these children had been enrolled in preschool special education programs.

In addition to being a large, population-based study, our study had a number of other strengths. We included a detailed review of case records by a panel of autism experts to confirm the case definition for autism according to DSM IV criteria. We were able to obtain additional clinical information that allowed us to evaluate associations within subgroups of case children according to developmental course (eg, regression) or presence of other coexisting conditions (eg, MR). We ascertained vaccination histories from standard immunization forms, eliminating possible recall bias. Information bias was further reduced by the fact that the clinical and behavioral data and the vaccination data came from independent record sources and the information on both exposure and outcome was recorded before the publicity about a possible association between MMR and autism. Furthermore, by linking with birth records, we were able to evaluate and control for potential confounding by demographic and birth characteristics.

Although the original group of 987 autism case children identified by MADDSP in 1996 probably was a fairly complete enumeration of cases in metropolitan Atlanta, we were able to locate vaccination records for only approximately two thirds of these children during 1999 through 2001. This is primarily because when a child moved or changed schools, the permanent school record was transferred to the child's new school and we did not have access to records for children who were no longer attending a school in a metropolitan Atlanta public school district that participates in MADDSP. Thus, factors related to moving or changing schools might have influenced our results. However, we did not find any significant differences in demographic characteristics or cognitive level between case children who were included and those who were excluded from the study.

Among case and control children whose records we were able to match with Georgia birth certificate files, we performed a subanalysis to evaluate possible confounding by differences in birth and maternal characteristics. For the most part, the results were not greatly different from those in the total sample. The differences that were noted were predominantly of lower ORs in the birth certificate sample. These differences seemed to be primarily a result of restricting the analysis to children who were born in Georgia and could be matched to a state birth certificate and not to confounding by maternal or birth characteristics. Thus, the differences between the 2 samples could represent random fluctuation or a possible bias related to being born outside Georgia.

A number of other epidemiologic studies have failed to find an association between MMR vaccination and autism.[19–24] A recent retrospective cohort study from Denmark is particularly persuasive.[24] The study contained data on more than half a million Danish children, including nearly 100 000 who had not been vaccinated with MMR. Through linkages of various national registries and medical databases, the study found that the relative risk associated with MMR was 0.92 (0.68–1.24) for autistic disorder and 0.83 (0.65–1.07) for other ASDs. An Immunization Safety Review Committee of the IOM[25] reviewed the epidemiologic and other evidence on MMR vaccine and risk for ASDs and concluded that the evidence favors rejection of a causal relationship at the population level. Other review panels have reached similar conclusions.[44,45] The IOM committee, however, did recommend additional studies to evaluate potential high-risk subgroups of children.

The caveat by IOM relates primarily to "autistic enterocolitis," which has been proposed by Wakefield and colleagues[16,18] to be a new clinical syn-

drome that is associated with MMR vaccination as supported by laboratory evidence of persistent measles virus infection in the intestines of affected children. The syndrome is characterized by developmental regression along with gastrointestinal disturbances. We were not able to evaluate the syndrome because we lacked information on gastrointestinal symptoms, but we did not find an association between age at vaccination, most notably by 18 months or 24 months, and autistic regression. We found a lower proportion of cases with regression, however, than has been reported in other studies.[40,46] Our number of regression cases is likely to be an underestimation because we relied on abstracted information rather than interview with the parent and we may not have captured all of the behavioral information needed to determine whether the child had regression. Analyses by other investigators have found no support for a new variant of autism[40,46] or for the association of the MMR vaccination with regressive autism[23] or gastrointestinal disorders.[47]

In addition to regression, we evaluated other clinical subtypes of ASDs, including case children with and without MR, and case children who did not have congenital malformations or early evidence of developmental problems (and thus were at risk for onset of developmental disabilities at the recommended age for MMR vaccination). We generally did not find increased risks for any of these case subtypes associated with MMR vaccination at any age. The only exception was that case children without MR were more likely to have been vaccinated before 36 months of age than their matched control children.

Other concerns have been raised about vaccinations and autism, especially about thimerosal, the mercury-containing preservative that until recently had been included in multidose preparations of certain vaccines.[25] In the present study, we were not able to evaluate the potential association between thimerosal exposure and autism. The routinely recommended infant vaccines that used to contain thimerosal were diphtheria-tetanus-pertussis, hepatitis B, and *Haemophilus influenzae* type b. Hepatitis B and *Haemophilus influenzae* type b vaccines, however, were not required for school attendance during the period of our study, and they were incompletely recorded in the school records. MMR vaccine has never contained thimerosal. Single-antigen measles vaccine has been hypothesized to be safer than MMR,[48] but we had too few children who received measles vaccine alone to be able to evaluate this possibility. We performed an analysis in which we evaluated associations with any measles-containing vaccine; the results were similar to those for MMR vaccine (data not shown). We did not evaluate associations with the second dose of MMR vaccine because it is usually administered between 4 and 6 years of age, which is after the 36-month age limit for autism onset as defined by the DSM-IV.[1]

CONCLUSION

From a large population-based case-control study that included a well-defined case group and a comparison group of children selected from the same community, we found that, overall, the age at time of first MMR administration was similar among case and control children. Case children, especially those 3 to 5 years of age, were more likely than control children to have been vaccinated before 36 months of age. A majority of case children who were vaccinated after 36 months of age, however, had indications of developmental problems before 36 months of age. The difference in vaccination coverage by 36 months of age between case and control children is likely to be an artifact of immunization requirements for preschool special education attendance in case children.

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DISAPPOINTING RESULTS

"Lack of a measurable analgesic effect and absence of a beneficial effect on poor neonatal outcome do not support the routine use of morphine infusions as a standard of care in preterm infants who have received ventilatory support. Follow-up is needed to evaluate the long-term effects of morphine infusions on the neurobehavioral outcomes of prematurity."

Simons SHP et al. Routine morphine infusion in preterm newborns who received ventilatory support. *J Am Med Assoc*. November 12, 2003

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Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta

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