Autism and Childhood MMR Vaccine
Analysis Plan

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Comments in margins.

April 3, 2001

Introduction

Autism is a serious life-long developmental disorder characterized by marked impairments in social interactions, and communication skills; and repetitive, restrictive, or stereotyped behaviors. A recent review of studies conducted since 1985, shows an estimate of the prevalence to be 1-1.4 per 1,000 for classic autism, and possibly as high as 4-5 per 1,000 for all autism spectrum disorders (ASD) combined (1,4). While these rates are 3-4 times higher than rates found in studies conducted 15-20 years ago (1), there are several recent studies, including a study done by Baird et al. (2000) and an investigation in Brick Township NJ, which suggested that the rate of autism may be higher still with rates of 3.1 per 1,000 and 4 per 1,000, respectively (CDC report; Baird study). These higher prevalence rates, coupled with reports of increasing numbers of children with autism being served by schools and service agencies (California report; DofED) have prompted concerns that the rate of autism may be increasing.

It has been suggested that vaccination, particularly with measles, mumps, and rubella (MMR) vaccine, may be related to the development of autism. The two main arguments that are used in support of a possible association are: 1) the prevalence of autism is increasing at the same time that infant vaccination coverage has increased; and 2) in some cases of autism, there is an apparent temporal association in which autistic characteristics become apparent within a few weeks to a few months after receipt of the MMR vaccine. Although the prevalence of autism and similar disorders appears to have increased recently, it is not clear if this is an actual increase or due to increased recognition and changes in diagnostic criteria. The apparent onset of autistic symptoms in close proximity to vaccination may be a coincidental temporal association.

A study published in 1998 in the Lancet (5) has lead some to hypothesize that the MMR vaccine may play a role in the recent trends in autism. This study was a case series of 12 children who were referred to a pediatric gastroenterology clinic because of chronic enterocolitis and the co-existence of autistic behavioral characteristics. Eight of the 12 children were reported by parental interview as first experiencing the onset of autistic-like symptoms following the MMR vaccine, and an additional child's onset occurred after measles infection which lead the investigators to hypothesize that the measles, mumps and rubella vaccine might be associated with the onset of autism. While suggestive, the clinical case study lacked evidence to evaluate a possible causal association between MMR and the occurrence of ASD (6).

Subsequent studies by Wakefield and colleagues were conducted to examine the potential association between inflammatory bowel disease (IBD) and autism. Wakefield's group and others have suggested that highly specific measles assays are in fact negative for measles virus in patients with IBD (FD 4-6) which was the posited biological mechanism for the described association between autism and the MMR vaccine. In addition, Wakefield et al. conducted an epidemiologic follow-up study of a 1970 British birth cohort in which no overall association was

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found between measles disease or measles vaccination and the subsequent occurrence of inflammatory bowel disease (i.e., ulcerative colitis or Crohn's disease) (FD-7).

Wakefield and collaborators have since proposed that they have identified a new syndrome consisting of milder gastrointestinal conditions, predominantly ileocolonic lymphonodular hyperplasia and mild intestinal inflammation, associated with behavioral regression (FD-8). They have reported identifying laboratory evidence of measles virus genome in the peripheral white blood cells and bowel biopsy specimens of a few such patients (FD-9,10).

Frombonne (1998) using two large databases, one, a clinical database from the Child and Adolescent Psychiatry Services of large teaching hospital in south London with about 9000 clinic records and the second a survey of autism in France in school-aged children in three French departments (from a population of 325,347 children) examined records of children with autism for the co-occurrance of ulcerative colitis or Crohn's disease. There were no cases that were identified in either database, suggesting that if these conditions are associated, as suggested by Wakefield et al. (1998) it was a rare occurrence.

Davis, Kramarz, Bohlke et al (2001) carried out a case-control study of individuals from four large health maintenance organizations in the United States. They identified 155 cases with ICD-9 IBD and up to 5 controls matched on sex, age, and HMO. Only 142 cases were subsequently used in the analyses of timing of vaccination and diagnosis of IBD. Of the 142 cases, 75 were Crohn's diseases and 67 had ulcerative colitis (UC). Ninety-four (66%) of cases had been vaccinated with MMR and 38 with other measles containing vaccines (MCV). Ten had never been vaccinated with either MMR or MCV. There were no statistical associations between timing of vaccination and subsequent diagnosis of IBD, Crohn's Diseases or UC at 2, 4, 6, or 12 months after vaccination.

A number of other studies have been carried out to try and confirm the association found between autism and the MMR vaccine. A study in Sweden, which used data from the only population-based registry of autism, showed that the prevalence of autism did not increase after the introduction of the MMR vaccine in 1982. (Gillberg & Heijbel, 1998).

Taylor et al., identified 498 autism cases (261 typical autism, 166 atypical autism, and 71 Asperger's syndrome) in eight North Thames health districts in the United Kingdom (UK) who were born since 1979. These cases were linked to an independent regional vaccination registry. The study examined time trends in rates of autism, comparison of age at diagnosis for children vaccinated before and after 18 months of age, and case series analyses examining temporal trends between MMR vaccination and age of onset. There were no statistically significant associations between onset of autism within 1 or 2 years after vaccination with MMR. Further, developmental regression was not clustered in the months following vaccination and no significant temporal clustering for age at onset of parental concern was seen for cases of core autism or atypical autism with the exception of a single interval within 6 months of MMR vaccination (7). There were several possible weaknesses in the study including failure to confirm ICD10 criteria for diagnosis of ASD and the possibility of incomplete ascertainment.

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Another study utilizing (8,9) a Finnish cohort of 1.8 million individuals with approximately 3 million MMR vaccine doses from 1982 to 1996 was examined. There were 173 potentially serious reactions that were claimed to be causally associated with MMR vaccination. Of these adverse events, 45% had evidence suggesting other causes or contributing factors (i.e, infectious agents, viruses). The resulting incidence of adverse events was 5.3 per 100,000 MMR vaccinees. There were no cases of autism that were associated with MMR vaccination.

In 2001, Kaye et al. (10) published a study in the British Medical Journal that examined children 12 years or younger from the UK diagnosed with autism between 1988 and 1999 through the use of the UK general practice research database. Because only 3% of children did not receive the MMR vaccine, time trend analyses were carried out to determine whether there was a temporal association between the MMR vaccine and the diagnosis of autism over time. A total of 305 autism cases aged 12 or younger whose first recorded diagnosis occurred between 1988 and 1999 were identified from 3,092,742 person year observations. Subsequent analyses were restricted to boys aged 2 to 5 years born between 1988 and 1993. Annual birth cohorts were analyzed separately. There was a significant increase in rates of autism between 1988 and 1999 from 0.3 per 10,000 person years in 1988 to 2.1 per 10,000 person years in 1999. There was no temporal association between MMR prevalence rates and risk for autism. The major weakness in the study is that diagnosis of autism was not confirmed from original records.

More recently, Dale et al., published in JAMA the results of a study done in California that was conducted to determine if a correlation exists between the trends of MMR vaccine coverage and autism occurrence. The researchers of this study performed retrospective analyses of children from kindergartens who were born in 1980 to 1994 (samples of 600-1900 children each year) and of autism cases derived from the California Department of Developmental Services who were born in the same years. School immunization records were reviewed to determine the age the children received the first dose of the MMR vaccination. Two main outcome measures were used: the proportion of children in each birth year that received the MMR vaccine by the age of 17 months and the proportion of children that received the vaccine by the age of 24 months. The results of this study showed no correlation between the trend in MMR vaccine coverage and the occurrence of autism. It was noted that there was a marked increase in autism from 1980 to 1994, 44 per 100.000 in 1980 to 208 per 100,000 in 1994; however, it was also found that changes in MMR immunization coverage were smaller and of shorter duration. ~~NIP is part of CDC (although I'm sure there may be those who may not see it that way)~~

In an effort to resolve the speculation about vaccinations and autism, the CDC in collaboration with the National Immunization Program, has conducted a matched case-control study utilizing the Metropolitan Atlanta Developmental Disabilities Surveillance Program to look at this potential relationship. The main objective of this study is to evaluate the association between the timing of the receipt of MMR vaccine and subsequent diagnosis of autism. The secondary objective will be to evaluate associations between other childhood vaccines and autism. This will include an examination of thimerosal exposure during the first year of life. ~~we can't be sure of this in all cases~~

The CDC's Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) monitors the rate of serious developmental disabilities using records from public school special education and other records for children with one or more of four developmental disabilities -- mental retardation, cerebral palsy, hearing impairment, and vision impairment. In the 1996

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surveillance year autism was added to the MADDSP in response to public concern about the possible increase in the prevalence of autism and related disorders. The first year of prevalence data for autism is completed with over 700 children with autistic disorder identified. The strengths of the MADDSP included the multiple source approach to identifying children with developmental disabilities and the expert clinical review of case information to determine eligibility. ~ complete population-based ascertainment is also a very strong feature

Justification for Study

A fundamental limitation of most of the previous investigations of the association between the MMR vaccine and autism has been the question of the completeness of case ascertainment and the lack of confirmation of the diagnosis of autism. Most of the studies described above used selected service provider databases to identify children with autism and did not confirm the diagnosis of autism from original records. These limitations coupled with the continuing concern that surrounds this issue suggests the need for further research to clarify the relationship between MMR vaccine and ASD. The benefits of the proposed study include 1) complete ascertainment of known cases from a large population, 2) extensive record review of cases to confirm the diagnosis of ASD, 3) inclusion of a sample of controls matched by age, sex, and school system to compare the distribution of age at MMR vaccination among cases and controls, 4) inclusion of birth records to control for other background variables that may be associated with autism including birth weight, gestational age, maternal age, and maternal education, and 5) because of the extensive clinical information on case children, the ability to examine the case group by the presence or absence of other co-existing conditions, e.g. mental retardation. It is expected that findings from this study will provide important information regarding the relationship between MMR and ASD.

Handwritten margin notes: - I'm not sure these apply to Taylor's study - Gillberg & Heijbel had very thorough ascertainment, but individual level vax. data not available - Taylor did not have individual controls

Study Design

We used a case-control design to examine the distribution of age at MMR vaccination among 3-10 years old children with autism compared to control children. Case children were identified through a population-based surveillance system used to assess the prevalence of five developmental disabilities including Autistic Disorder. Control children were selected from the same population as the case children and matched on birth year, gender, and school system.

Study population

MADDSP was established to ascertain all children who have one or more of the five developmental disabilities -- mental retardation, cerebral palsy, autism, hearing impairment, and vision impairment -- who are 3 to 10 years of age and whose parents reside in the five-county metropolitan Atlanta area. In 1996, this area had an estimated population of 2.5 million people, approximately 38,000 live births per year, and 289,456 children 3-10 years of age.

Cases:

Information about children with autism was obtained through review of education and clinical records. Children with Rett's Disorder or Childhood Disintegrative Disorder were excluded as

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autism cases; however, information on these children was maintained in the database. Information on potential cases was collected via a multiple-source case finding method of record abstraction. Children's records that contain descriptive behavioral information, diagnostic tests, and other relevant diagnostic information were abstracted at different sites including school systems (special education records) and public and private clinics that serve children with autism.

A behavioral coding system based on the Social, Communication, Behavioral, and age criteria, as well as the Associated Features for Autistic Disorder was developed (who developed this?). Based on review of each child's evaluation reports (information abstracted from medical, psychological, educational reports from the source records), each sentence describing the child was scored based on the DSM-IV criteria. A randomly selected set of the records (20%) was independently scored by a second reviewer to determine reliability of the classification system of ASD cases.

A panel of professionals who have extensive experience in the field of autism made the diagnosis of autism. Each child's abstracted records were reviewed and scored for case definition behaviors by a team of four expert reviewers. The reviewers consisted of 2 developmental psychologists, a clinical psychologist, and a special education specialist. The cases that were found questionable after review were then reviewed by Catherine Lord, a ......, for a final diagnosis.

[handwritten: Wow! You can't get any better than this!]

For the purposes of MADDSP, children who met the autism case definition included:
- As in DSM-IV, children who had at least 6 of the behavioral criteria (including at least 2 in the Social, 1 from Communication, and 1 from the Behaviors/Interests domains);
- Children who met less than 6 behavioral criteria, but whose scored behaviors included at least 1 relevant Social behavior and either 1 behavior from the Communication and/or 1 from Behaviors/Interests domains;
- Children with the appropriate number of criteria but whose records did not have information about an early delay before the age of 3 were included as ASD, but the lack of age criterion was noted.

[handwritten: This is a bit confusing (? redundancy/conflicting)]

An ASD case was defined in MADDSP as a child: (1) who was 3-10 years old at any time during 1996; (2) whose parent or legal guardian resided in the five-county metropolitan Atlanta area during 1996; and (3) who displayed behaviors (as described by a qualified professional) consistent with the DSM-IV diagnostic criteria for Autistic Disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) or Asperger's Disorder [DSM-IV reference]. In the absence of described behaviors, we considered a child to have ASD if he or she was given a diagnosis (impression ???) of ASD by a qualified examiner (e.g., psychologist, developmental pediatrician).

[handwritten: Possibly drop]

For the purposes of this paper we have dichotomized the ASD cases into two groups: Autistic Disorder (N=810) and Atypical Autism (N= 78), which includes cases diagnosed with PDD-NOS and Asperger's Disorder. Children diagnosed with PDD-NOS and Asperger's Disorders were grouped together due to the small number of children with these diagnoses.

[handwritten: ? definition different (is this different from what is listed above?)]

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Controls:

Control children were selected from the same population as cases and were matched based on age within XXX months, sex, and school system (county school system or actual school). The ratio of controls to case was chosen to be 3:1 (N=539). For a small number of cases (N=11), fewer than three controls were obtained but these cases and controls will still be included in the analyses. Controls were selected from the regular education programs and were not receiving special education services at the time of abstraction.

During the time of abstraction, it was not possible to verify whether or not many of the controls received special education services, at some time in the past, prior to enrollment at the school where the child's record was abstracted. Therefore, after controls were abstracted they were checked against the MADDSP during the study years of 1991 through 1994 and study year 1996 and were also matched with the Georgia Special Education Files by the child's last name, first name, and birth date. While none of the 1,640 controls were found in the MADDSP, 111 (7%) were found in Georgia's Special Education files. These controls will be excluded from the study on the basis that their vaccine history and experience may be different than non-affected control children.

Vaccination history:

Trained abstractors collected vaccination histories of cases and controls from the standardized State of Georgia immunization forms that all children are required to provide to attend public schools in Georgia (See Appendix " "). The immunization form, also referred to as Form 3032, reflects the immunization requirements (minimum standards) for attendance at Georgia schools (See Appendix ' '). The forms are filed in each student's permanent school record. The child's primary care physician completes the forms prior to school entry. All administered childhood vaccinations and dates of vaccination are recorded in the vaccination forms. The abstractors collected the vaccination dates and organized them in chronological order; however, a majority of the time they were already recorded in the order they were administered. Other information collected from the vaccination forms includes the parent and child's names, location of vaccine administration, the physician or qualified examiner who administered the vaccine, and information regarding the administration of vaccines not required for school entry or additional doses of a vaccine that was required. Data regarding vaccination exemptions (medical and religious) was also available; however, no children in this study had obtained a vaccination exemption for any reason.

Family Background and Other Data Collection:

Information was extracted from the child's school record including child's date of birth, sex, birth state, and race. We matched case and control children born in Georgia to the State Birth Certificate files. Approximately, 50% of the controls have been successfully matched with the Georgia Birth Files and 63% of cases have been matched with Georgia birth file. The matching criteria that was used was birth certificate number, child's first and last name. For the subset of children with Georgia birth records we will perform a sub-analysis in which we will adjust for

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key variables from the birth certificate (e.g., birth weight, gestational age, maternal age and education, etc.)

Additional background information was obtained from MADDSP for case children. This included information on the presence of other developmental disabilities (mental retardation, cerebral palsy, vision and hearing impairment, and epilepsy), the presence of a coexisting medical condition (specifically, tuberous sclerosis and fragile X syndrome) and IQ functioning. In addition, we identified major congenital malformations among the case children by matching with the CDC's Metropolitan Atlanta Congenital Defects Program.

Exposure Variables

Several factors need to be considered in examining the association between the receipt of the MMR vaccine and development of Autistic Disorder. First, the National Immunization Survey data indicate that for the birth years covered by this study, between 83 and 91 percent of children between 19 and 35 months of age will have received MMR vaccine. Data from this study show that approximately 82% of cases and controls have been vaccinated by 24 months. Because all children in Georgia must document receipt of the MMR vaccine before school entry, there will not be an unvaccinated referent category. Therefore, the primary exposure of interest in this study will be the timing of the receipt of the MMR vaccine. The timing of MMR vaccination will be examined in at least three different ways. First, we will categorize children according to whether they were vaccinated before or after age 24 months. We have selected 24 months as the age cut-off because a diagnosis of autism requires onset of one of the defining behaviors before 36 months of age and the biological plausibility of an exposure creating such symptoms would require a significant amount of time to manifest itself. Second, we will perform an analysis with age of MMR vaccination more finely categorized to further explore possible associations between age at vaccination and autism. The ages at vaccination will be categorized as: 6-11 months; 12-15 months; 16-18 months; 19-24 months; 25-35 months; ≥ 36 months.

Make consistent with Table 3

Prior to 1999, thimerosal was included as a preservative in most multi-dose formulations of DTP, hepatitis B and Hib vaccines. To the extent possible, thimerosal exposure will be investigated (e.g, cumulative exposure at 3 months of age). The cumulative exposure at 3 months was chosen for several reasons: 1) since 1991 ACIP has recommended that children be vaccinated with the first dose of Hepatitis B, DTP and Hib by 2 months of age, 2) independent of whether the Hepatitis B vaccine is administered at birth or later, the weight adjusted thimerosal exposure following ACIP guidelines is highest at 2 months of age, and 3) a recent study of thimerosal exposure carried out by the CDC suggests that thimerosal exposure at 3 months of age is predictive of several neuropsychological outcomes (ADHD and language and speech delay). Since important information regarding the vaccine manufacturer lot number will be unavailable, it will not be possible to calculate exact levels of thimerosal exposure. We will approximate thimerosal exposure for each child based on a weighted average of the amount of thimerosal found in each the three vaccines that included thimerosal prior to 1999. The majority of children in this study will have been vaccinated prior to 1991 and therefore will not have been exposed to thimerosal from the hepatitis B and Hib vaccines during the first year of life.

[handwritten annotations in margins:]

Unless they got a medical or philosophical exemption

Wakefield's cases recurred within ~7 days

– Could note that regression usually occurs before 24 months

may be — Although these other associations were also found at other ages

– CAN (Bernard, Redwood) focuses on 6 month cumulative exposure

may want to look at cumulative thimerosal at 3 mos. and 6 mos.

[handwritten diagram/notes at bottom: Hib 24 months 1991 DTP Dose 3, 3 X months, went to Doses]

A000035

Other exposure factors to be considered will include the total number of vaccines the child received and number of total doses for each vaccine given by 12 months, 24 months and 36 months of age. *May also want to add total number of vaccine antigens received by these ages.*

Add Antigen [handwritten]

Statistical Analyses:

We will use conditional logistic regression stratified by matched sets to estimate the odds ratios for the association between age at MMR vaccination and autism. In the main analyses, we will include all autism cases.

For the children born in Georgia for whom we have birth certificate data, we will perform several sub-analyses similar to the main analysis, and will include several additional potentially confounding variables. There will also be additional data from the Metropolitan Atlanta Congenital Defects Program that will be included in the sub-analyses. The variables that will be evaluated will include:

← as potential confounders [handwritten]

Birth weight
Gestational age
Birth type (singleton, twin, etc.)
Birth order
APGAR scores (1 and 5 minutes)
Maternal age
Maternal education
Maternal race
Maternal parity
Congenital anomalies of child **(from MACDP)**

Each of the above variables will be individually evaluated for their association with autism disorders. Those with an odds ratio p-value < 0.20 will be included as covariates in a conditional logistic regression model to estimate adjusted odds ratio for the association between age at vaccination and autistic disorder.

Analysis of Autism subgroups

We will conduct the following sub-group analysis of the study population:

need to state what the outcome event will be (1st diagnosis, 1st parental concern, 1st symptom?) [handwritten]

1) Analysis restricted to autism cases/case-series analysis *← regression* [handwritten] ***
2) Analysis restricted to male autism cases
3) Analysis excluding cases with an established cause for autism (e.g., congenital anomaly/chromosomal abnormality, fragile X, tuberous sclerosis etc.)
4) Analysis of autism cases subdivided into isolated and non-isolated autism subgroups

Will you test for interaction bt gender? [handwritten, left margin]

Sorry, I see it is on the next page [handwritten, right margin]

We will not subdivide the autism cases by summary diagnosis due to the small number of cases diagnosed with ASD-NOS (N=36). A majority of the cases received a diagnosis of autistic disorder (N=495)

We should do a separate analysis of "autistic disorder" (not clear if this is meant in #1 above) [handwritten, bottom left]

* I'm not sure there is a need to do this because the case-series approach was one of the main criticisms of the Taylor 8 study. Also, probably best suited for regression + we don't have good data on this. [handwritten, bottom right]

A000036

Cases Series Analyses of Autistic Disorder Cases

We propose using age of first evaluation as an outcome measure in a case series type of analysis. Onset of autism is extremely difficult to define even with very complete information. Moreover, the special education and other records that were used to identify, define, and categorize the cases did not always contain information on when the constellation of behaviors characteristic of autism was first noted. Assuming we can develop a reliable and valid measure of age of first evaluation, we ~~replicate the~~ case series analyses carried out by Taylor et al.

[handwritten: will perform a similar as]

Analysis of Male Autistic Disorder Cases

[handwritten: previous page "autistic disorder" total listed as 495 Anyway)]

Among the autistic disorder cases there were 446 males to 112 females. Therefore, subsequent including only the 446 male cases will be conducted in order to examine whether temporal associations between vaccinations and the age of first evaluation are different from all autistic disorder cases.

[handwritten: these numbers refer only to what we currently have in hand. Presumably more will be available in the final analysis.]

Analysis Excluding Cases with an Established Cause for Autistic Disorder

We propose to conduct analyses looking at cases without an established cause for autistic disorder such as tuberous sclerosis, fragile X, and other congenital/chromosomal anomalies. The purpose of doing this analysis is to see whether or not these cases differ in their vaccination history patterns and experience then children with an established cause. *[handwritten: Also, less biologically plausible that cases with established cause could be related to vaccination.]*

Analysis of Autistic Disorder Cases Subdivided into Isolated and Non-isolated Autistic Disorder Subgroups

[handwritten margin: I'm not aware that the genetics on results an affirmed difference by absence of MR. Is this well established?]

Subsequent analysis examining potential differences between the isolated and non-isolated autistic disorder subgroups will be conducted. We have found that approximately 80% of the cases in the non-isolated subgroup have a co-existing disability of mental retardation, which has been found to have a genetic origin. Therefore, this group may show different trends in vaccination patterns when compared to the isolated autistic disorder group. *[handwritten: check]*

Study Strengths and Limitations:

Strengths:

- Population-based study with fairly complete ascertainment of autistic disorder cases in a well-defined geographic area.

- Extensive record review of cases to confirm the diagnosis of autistic disorder and atypical autism.

- Standardized form for MMR vaccine exposure information that was completed by the child's primary care provider.

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- We have identified 742 cases of autistic disorders for inclusion in the study. With 3 matched controls per case, 90 % vaccination coverage among controls, .05 alpha error, we will have 80% power to detect an odds ratio of about 1.6 at the lowest. We will have 90% power to detect an odds ratio of about 1.8. If exposure among controls is as high as 95%, we will have 80% power to detect an odds ratio of 2.0.

[handwritten margin note: Should have a separate sample size/power section]

- Matching with birth certificates allows controlling for several potentially confounding factors such as birthweight, gestational age, maternal age, and maternal education.

Limitations:

- Retrospective study with information on cases restricted to what is available in various records.

- Inherent in this type of record review are errors that cannot be rectified through use of an independent data source. Care was taken to record the information accurately with edits done by the computer programmer, the abstractors, and the project coordinator. However, it was decided that several of the Immunization forms contained errors in dates that could be reasonably corrected (e.g., transposition of year digits 98 for 89) whereas others that could not be corrected and will be counted as missing data. This will be reflected by the numbers of case/control children with complete information available for analyses.

- Date of onset or first occurrence of characteristic behaviors incompletely recorded.

- Incomplete ascertainment of all autism spectrum disorders, especially Asperger's Syndrome and high functioning autistic disorders.

Table Shells:

Table 1 Descriptive characteristics

		Cases		Controls	
		N	%	N	%
Sex	Male				
	Female				

Age in 1996 *(birth year)*
        3-5   (1991 - 1993)
        6-8   (1988 - 1990)
        9-10 (1986 - 1987)

Race
        White
        Black
        Other

(Georgia?)

Birth Certificate Factors (Subset- those born in metro-Atlanta)
        Birth Weight
        <1500 gms
        1500-2499 gms
        2500+ gms

        space Gestational Age — ? categories (?, <38 wks, 38 - 42, >42)
        Birth Type
        Singleton
        Twin
        Triplet+

        Maternal Age
        <20
        20-29
        30-34
        35+

        Maternal Education (years)
          <12
           12
           13-15
          ≥ 16

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Table 2 (actually maybe better as Table 1) Clinical features of cases

Co-existing developmental disabilities:
Mental Retardation (level) — ? available
Cerebral Palsy
Vision Impairment
Hearing Impairment
Epilepsy

Associated medical conditions:
Genetic:
      FRAX
      Down Syn
      Tuberous Sclerosis
      Turners Syn
      Other Chrom or single gene
      Metabolic disorders
Infections:
      CRS, etc.
      Meningitis-neonatal, early childhood
Exposures:
      FAS
Other CNS:
      Trauma

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Table 3 Association between age at vaccination and autism

Age vaccinated	Cases	Controls	OR (95 % CI)
<24 mos	n (%)	n (%)	
≥24 mos	n (%)	n (%)	1.0 (referent)
6-11 mos			
12-15 mos			
16-25 mos			
26-35 mos			
≥36 mos	n (%)	n (%)	1.0 (referent)

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