Comparison of Age at First MMR Vaccination among Children with Autism and School-matched Controls in Metropolitan Atlanta

Preliminary DRAFT

Preliminary Results

Not For Circulation

October 28th, 2002

Abstract

Introduction

We conducted a matched case-control study utilizing the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Developmental Disabilities Surveillance Program. The main objective of the study was to evaluate the association between autism and age of receipt of the MMR vaccine after controlling for background characteristics. We also examined several autism cases subgroups to determine if more homogenous subgroups were more vulnerable to the potential negative effects of early vaccination with the MMR vaccine.

Methods

The CDC's Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) was used to identify children with autism (N=625) who met the MADDSP surveillance case definition for autism and had school vaccination records with vaccination dates available from one of 9 school systems in the 5 county Atlanta surveillance region. Control children (N=1,824) were selected from regular education programs and were matched to case-children based on age, sex, and school of attendance at the time of abstraction. Trained abstractors collected vaccination histories for both cases and controls from the standardized State of Georgia immunization forms that all children are required to provide to attend public schools in Georgia. The primary exposure of interest was age of receipt of the first dose of the MMR vaccine. We used conditional logistic regression models stratified by matched sets to estimate the odds ratios for the association between age at MMR vaccination and autism. Confounding variables available from the birth certificate were evaluated for their impact on the MMR-autism association.

Results

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. Recent studies have suggested that the prevalence of autism is higher (30–60 per 10,000 persons) (Baird et al., 2000; Bertrand et al., 2001; Yeargin-Allsopp et al., 2002) than in studies conducted 15-20 years ago (4-5 per 10,000; Fombonne, 1999). The apparent increase in prevalence, coupled with reports of increasing numbers of children with autism being served by schools and service agencies (ref: school special ed data; Croen 2002) have prompted concerns about the possible role of environmental factors. Vaccines, particularly the MMR vaccine, are among the exposures about which there has been the most speculation of a possible association with autism. The U.S. vaccination schedule recommends that children be vaccinated with the MMR vaccine between 12 and 15 months of age (ref: ACIP), which coincides temporally with the usual age at which atypical development is first noted in children with autism.

Wakefield and colleagues have proposed that MMR vaccine may be linked to the cause of autism. They published a study describing 12 patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism (Wakefield et al, 1998). In 8 of the 12 cases, the children's parents or pediatricians suggested that MMR vaccine contributed to the onset of behavioral problems. The authors hypothesized that MMR vaccine was responsible for bowel dysfunction (enterocolitis) and subsequent neurodevelopmental disorders. They have proposed a new syndrome consisting of certain gastrointestinal conditions, predominantly ileocolonic lymphonodular hyperplasia and mild intestinal inflammation, associated with behavioral regression (Wakefield, Anthony, et al, 2000) and reported identifying laboratory

evidence of measles virus genome in the peripheral white blood cells and bowel biopsy specimens of a few such patients (Kawashimi et al, 2000; Torrente et al. 2002; Uhlmann et al., 2002). Since the initial publication of the Wakefield report, several epidemiologic studies have not found an association between MMR vaccination and autism (Dales et al, 2001; Farrington et al 2001; Gillberg et al, 1998; Kaye et al, 2001; Taylor et al., 1999; Denmark 2002). The Institute of Medicine (IOM: 2001) reviewed the MMR-autism hypothesis and rejected a causal association at the population level, but encouraged additional studies to more fully evaluate the possibility that there may be an association between MMR and autism in certain subgroups of children.

We conducted a matched case-control study utilizing the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP). The main objective of the study was to compare MMR vaccination histories of a population-based sample of children with autism and school-matched controls who did not have autism. We also evaluated associations between MMR and autism in subgroups of children and according to the presence of different clinical or behavioral manifestations of the disorder.

Methods

Study population

Children with autism were identified from MADDSP, a multiple-source, population-based surveillance program that monitors the occurrence of selected developmental disabilities among children in the five-county metropolitan Atlanta area (Yeargin-Allsopp, M. et al., 2002). MADDSP was established to ascertain all children 3 to 10 years of age, whose parents resided in the five-county metropolitan Atlanta area, and who had one or more of the following

developmental disabilities: mental retardation (MR), cerebral palsy, hearing loss, vision impairment, or autism.

Selection of cases and controls

In 1996, MADDSP identified 987 children with autism through the screening and abstraction of source files at schools, hospitals, clinics, and specialty providers (Figure 1). The case definition for autism spectrum disorder (ASD) was based on DSM IV criteria. Clinical psychologists or developmental pediatricians (check) with expertise in the diagnosis of autism reviewed the abstracted records according to standard procedures to determine the presence of behavioral characteristics consistent with DSM IV criteria for ASD (check) (ref: MYA 2002).

For the current study, during 1999 through 2001, we abstracted school immunization records of the cases originally identified in the 1996 school year. School records of case children were searched across all participating school systems in order to identify their school of enrollment at the time of abstraction. We were able to locate school records with the required immunization documents for 660 case children. The 327 case children whose school records were not found had either moved out of state, transferred to a school in a county that is not under MADDSP's jurisdiction, transferred to a private school that is not accessible by MADDSP, or were being home schooled.

We attempted to match 3 controls to each case and were successful for 97% of the cases, while the remaining 3 percent of cases had fewer than 3 matched controls. For 13 cases, we could not identify any matched controls and they were deleted from the study. Control children (N=1,891) were selected from regular education programs and were matched to case-children

based on age (? within one year), sex, and school of attendance at the time of abstraction. However, if a case-child was attending a psychoeducational school, a special school for children with behavioral and developmental difficulties including autism, controls were selected from the case-child's home school. A child's home school is the school in the child's residential area that the child would attend if the child did not have a disability at the time of abstraction. In addition, if a case-child was older than other children in their class and was in the last elementary grade level prior to middle school due to their disability, control children were selected from the middle school they would normally attend and would be matched to the case based on the established matching criteria.

We excluded cases and controls from the study if they were missing a vaccination form, unless they had a religious or medical exemption on file. We accepted vaccination forms as valid as long as they listed the administration of at least one diphtheria-tetanus-pertussis (DTP) vaccine by age 2 years or at least one MMR vaccination at any age. After exclusion, 624 cases and 1,824 controls remained in the study.

Vaccination history

Trained abstractors collected vaccination histories for both cases and controls from the standardized State of Georgia immunization forms that are required for all children who attend schools in Georgia. The forms are filed in each student's permanent record file that is kept at the school where the child is enrolled. During the period in which children in this study would have received their first MMR vaccine, Georgia law required at least one dose of measles, mumps, and rubella vaccine in the form of the MMR, MR, or single antigen vaccines at entry into elementary school. Effective with the 1994-95 school year, for entrance into the sixth grade of

school, a child needed to have received at least one additional dose of the MMR vaccine, for a total of two MMR vaccines administered on or after the child's first birthday and at least one month apart. Data regarding medical and religious vaccination exemptions were also recorded.

Other Data Collection

For children with autism, additional disability related information was obtained from the MADDSP data files. This included information on the presence of other developmental disabilities, epilepsy (a major associated medical condition of autism), other co-existing medical conditions, and level of cognitive functioning. In addition, we identified major congenital malformations among the case children by matching with CDC's Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based surveillance program of major structural malformations that covers the same geographic area (Edmonds et al, 1981).

For both cases and controls, demographic information including date of birth, gender, birth state, and race/ethnicity was obtained from the birth certificate that is kept in the child's permanent school record. Like the vaccination form, all children must provide the school of enrollment with the birth certificate for entry into elementary school; the presence of a birth certificate is not mandatory for those entering middle school. For the records that were abstracted at middle schools and were missing their birth certificate, a school registration form was used to obtain the necessary demographic information.

Subsequently, 355 cases and 1,020 controls born in Georgia were matched to state birth certificate records in order to derive more information on child and maternal characteristics, such as the child's birth weight and gestational age and the mother's parity, age, race, and education.

MMR Exposure Variable

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 relationship with MMR vaccination by examining the temporal relationship between vaccination and onset of initial parental concern, date of first diagnosis, or onset of regression (if present). We had incomplete information on these events, so we chose to compare the distribution of ages at first MMR vaccination between cases and controls. First we compared the overall distributions of age at vaccination. We then analyzed associations using three specific age cut-offs: 1) 18 months – as an indicator of "on-time" vaccination according to the recommended vaccination schedule for MMR vaccine; 2) 24 months – the upper age limit by which atypical development usually manifests in children with autism (Fombonne 2001, Short 1998, DiGiacomo 1999, Taylor 1999, Volkmar 1985); and 3) 36 months – the age by which autistic characteristics must have developed to meet DSM-IV criteria for autism (ref: DSM IV).

Classification of Autism Subgroups

In an effort to examine differing effects of the MMR vaccine in various subsets of children with autism, we reviewed the records of case children with an indication of delay prior to their third birthday to identify additional information that would allow classification of cases into subgroups that may have different susceptibility to potential adverse effects of MMR vaccine. We were particularly interested in children without an indication of delay before one year of age and without a pre-existing condition (e.g., congenital birth defect) that could contribute to developmental delays. Indication of developmental delay at less than one year was determined by whether or not the child had developed *any* speech at appropriate ages, including

cooing and babbling and whether or not the child was socially responsive in the first year of life (e.g., cuddling, appropriate eye contact, responding to parents voices). Furthermore, type of developmental concern was categorized as delay, regression, or plateau. We also attempted to collect information on age at first parental concern, and family history of autism and related autism spectrum conditions or other developmental disabilities, but this information was incompletely recorded and not useful for analysis.

Statistical Analyses

We used conditional logistic regression models stratified by matched sets to estimate the odds ratios for the association between age at MMR vaccination and autism. In the subgroup of children that we were able to match to birth certificate files, we were also able to adjust for other factors. Potential confounding variables were evaluated individually for their association with autism case status. Those with an odds ratio p-value < 0.20 were included as covariates in conditional logistic regression models to estimate adjusted odds ratios for the association between age at vaccination and autism (Maldonado and Greenland).

Results

Case selection

The 624 cases included in the analysis because we were able to locate their school records and the 327 cases whose records we could not find were similar with respect to age, sex (check), and cognitive functional status (Table 1). [check race distributions for the whole sample of 624 included vs. 327 excluded cases.]

Clinical Features of Autism Cases

Among the 624 cases, there were 378 with MR, 31 with cerebral palsy, 8 with visual impairment, 7 with hearing impairment, 49 with epilepsy, and 5 (check) with other birth defects. A total of 235 cases were identified with at least one pre-existing condition (? For example …). There were 80 cases that were identified as having a regression or plateau in developmental milestones after 12 months of age based on record review.

Demographic Characteristics of Cases and Matched Controls

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

The similarities in age and sex carried over to the 355 cases and 1,020 controls that were matched to the Georgia birth certificate files (Table 2). In this sub-sample, the racial distributions of cases and controls were the same and there were no children with missing race data. Using

data that was only available in the birth certificate files, however, we did find several differences between cases and controls. Compared with controls, case children were more likely to have had a low birth weight (p<.XX) and to have been the product of a multiple birth pregnancy (p<.XX). At the time of delivery, mothers of case children tended to be older (p<.XX) and to have had higher levels of education (p<.XX).

Comparisons of ages at MMR vaccination

The overall distributions of cases and controls at age of first MMR vaccination were similar (p=0.17) (Figure 2). Most children in both groups were vaccinated at 12 to 17 months of age.

When we performed the analyses dichotomizing age at vaccination, we found that vaccination prior to age 18 months or 24 months was not associated with case status, either overall or in the different sex or age subgroups (Table 3). The largest OR (1.66), although not statistically significant, was found in the 3 to 5 year old age group for vaccination before 24 months. Using a 36 month cut-off, there was a significant difference between cases and controls (OR=1.49), with the association being most pronounced in boys (OR=1.67 –check) and in children 3-5 years of age (OR=2.34 – check).

In the birth certificate sub-sample in which we were able to adjust for potentially confounding variables, there continued to be no significant associations with vaccination before 18 months or 24 months (Table 3). Except for the 3-5 year age group vaccinated before 24 months, all the odds ratios were decreased compared with those for the total sample. None of the results for the 36 month cut-off were statistically significant in the birth certificate sample. The OR for all cases in the birth certificate sample (1.23) was decreased relative to the total sample

(OR=1.49), suggesting that there may have been some confounding of the total sample results. The point estimates of the odds ratios in the birth certificate sample were little different from the total sample for boys and for the 3 to 5 year age group.

Results for different case subgroups

When we performed the analyses within different clinical case subgroups, we found no associations with vaccination before 18 months or 24 months of age among cases without pre-existing conditions before one year of age, cases with regression or plateau, and those with and without mental retardation (Table 4). The odds ratios varied between 1.07 and 1.37 and all of the confidence intervals overlapped 1.0. In similar analyses using a 36 month cut-off, all of the odds ratios tended to increase, but only the result among cases without mental retardation (OR=2.45) was statistically significant. All adjusted results using the birth certificate sample were not statistically significant. The main suggestion of possible confounding from the adjusted analyses was that all the odds ratios for regression or plateau decreased to less than 1.0, but with only 31 such cases the results were unstable and may have simply reflected random fluctuation. In the birth certificate sample, only 3 cases without mental retardation were vaccinated after 36 months of age resulting in a highly unstable odds ratio estimate for this subgroup.

Results according to race, birth weight, and maternal characteristics

We further examined associations according to selected sociodemographic and birth characteristics that were available from the birth certificate files. To perform these stratified analyses, we were not able to maintain the additional stratification for the matching variables (age, sex, and school), although we did adjust for the matching variables in the regression

models. Not stratifying on the matched sets allowed us to use a few more cases and controls for whom we had birth certificate data but had previously had to delete because their corresponding matched cases or controls were not able to be matched to the Georgia birth certificate files.

For all 355 cases included in these analyses, the association with age at vaccination was not significant for any of the three age cut-offs (Table 5). For vaccination before age 18 months or 24 months of age, nearly all of the odds ratios according to different categories of race, birth weight, maternal age, and maternal education were less than 1.0, but all the confidence intervals overlapped 1.0. For the 36 month cut-off, there were suggestions of possible associations within the subgroups of children whose mothers were older or had more years of education, but the confidence intervals for these results were very wide and overlapped 1.0 by a considerable margin.

Discussion

In this population-based study in a large U.S. metropolitan area, we found that the overall distribution of ages at MMR vaccination among children with autism was similar to that of school-matched control children who did not have autism. When we analyzed associations according to different age cut-offs, we also found that similar proportions of cases and controls had been vaccinated before 18 months or before 24 months of age. No significant associations for either of these age cut-offs were found for specific case subgroups, including regression. Delayed vaccination beyond 36 months was less common among cases than controls, although only a small proportion of children in either group received their first MMR vaccination after 36 months of age.

In addition to being a large, population-based study, our study had a number of other strong features. We conducted a detailed review of case records by a panel of autism experts to confirm the case definition for autism and obtain additional clinical information. The clinical detail allowed us to evaluate associations within sub-groups of cases according to developmental course (e.g., regression) or presence of other co-existing conditions (e.g., mental retardation). We ascertained vaccination histories from written records eliminating possible recall bias. Information bias was further reduced by the fact that the clinical data and the vaccination data came from independent record sources and the information on both exposure and outcome was recorded prior to the publicity about a possible association between MMR and autism. 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 ASD cases identified by MADDSP in 1996 probably was a fairly complete representation of cases in metropolitan Atlanta, we were only able to include in our study the 660 cases (67%) for which we could locate vaccination records. Comparison of included versus excluded cases indicated that they had similar sex and age characteristics, but the included cases were more likely to have had indications of mental retardation or low cognitive functioning. Thus, selection factors may have influenced our results to some extent. We evaluated possible confounding by differences in birth characteristics and maternal factors between the included cases and controls by performing a subanalysis among children that we were able to match with Georgia birth certificate files. For the most part, the point estimates of the odds ratios in the birth certificate sample were not greatly different from the total sample. The differences that were noted were predominantly of lower odds ratios in the birth certificate sample, suggesting that there may have been some modest upward confounding of the odds ratios in the total sample.

Our study was based on school records and was limited by the availability of information in the records. The main impact this had on the study was incomplete information for determining date of onset of autism. Determining onset of autism, however, is difficult even under the best of circumstances. In most cases, neurological defects associated with autism probably occur prenatally (Rodier 1998, Kemper and Bauman 1998, Nelson 2001), but parents may not become aware of any problems until later in life when communication delays and characteristic behaviors become apparent. Another limitation of our study was that almost all the children had received MMR vaccine as a requirement to attend school. Lacking an unvaccinated group and

information on date of onset, we chose to compare the distribution of ages at vaccination between cases and controls.

We found that the overall distributions of ages at MMR vaccination were not different between the cases and their matched controls. Similar proportions of cases and controls were vaccinated according the recommended schedule or before the usual ages at which atypical development manifests in children with autism. The U.S. vaccination schedule recommends that the first dose of MMR vaccination be administered between 12 and 15 months of age. Thus, our results for vaccination before 18 months of age evaluated possible increased risks of autism associated with vaccination around 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 (Fombonne 2001, Short 1998, Taylor 1999, DiGiacomo 1999, Volkmar 1985) and developmental regression usually is noted between 12 and 24 months of age (Lord 1995, Taylor 1999, Shinnar 2001, Tuchman and Rapin 1997). In Wakefield's case series, 10 of the 12 children had ASD (including one child with questionable ASD or childhood disintegrative disorder). Nine (90%) of the cases had atypical behaviors noted by 21 months and one between 4 and 5 years of age. Thus, we would expect that exposures that could be causally associated with autism would most likely occur before 24 months of age.

Cases in our study were more likely than controls to have been vaccinated before 36 months of age, which is the age by which atypical development must have had onset to meet the DSM IV criteria for autism. Since by 36 months the case children must have had some manifestations of atypical development, rather than representing causal associations, associations with the 36

month cut-off would be more likely than associations with earlier age cut-offs to have been influenced by factors related to the evaluation, management, and treatment of the child. For example, it is likely that after concerns about development arose, case children would have had more contacts with the health care system and had more opportunities to have had their vaccination status checked and to receive recommended vaccinations. In addition, case children may have been more likely to have been vaccinated as a requirement for enrollment in early intervention special education programs. This possibility is supported by the finding that the difference between cases and controls in the proportion vaccinated before 36 months of age was strongest in the 3 to 5 year old age group. As of 1991, IDEA has mandated the provision of early intervention education programs beginning at about 36 months of age for children with developmental disabilities, including autism (check). Thus, the children who were 3 to 5 years of age in 1996, would have been most impacted by the IDEA early intervention requirement.

Other epidemiologic studies have failed to find an association between MMR vaccination and autism. A recent retrospective cohort study from Denmark is particularly persuasive (ref NEJM 2002). The study contained data from 1991 through 1998 on over half a million Danish children, including nearly 100,000 who had not been vaccinated with MMR. Linkages with various national registries and medical databases were used to identify autism cases and dates of diagnosis, MMR vaccination dates, and key demographic and birth data. 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 autism spectrum disorders. Another population-based study by Taylor and colleagues identified

all 498 known ASD cases in a district of London and linked them to an independent regional vaccination registry (Taylor 1999). At age two years the MMR vaccination coverage among the ASD cases was nearly identical to coverage in children in the same birth cohorts in the whole district, providing evidence of an overall lack of association with vaccination. The study also evaluated incidence of autism within pre-defined time periods after vaccination using three different measures of autism onset (date of diagnosis, date of first parental concern, and date of regression) and no statistically significant associations were found, except for a small increased relative incidence (1.48) for initial parental concern within 6 months following vaccination. Further follow-up of this cohort has continued to find no evidence of an association between MMR vaccine and autistic regression (Farrington 2001).

Three other published studies also provide evidence against an association between MMR and autism. A study in Sweden found no increase in autism among children born after the introduction of MMR vaccination compared with those born before (Gillberg 1998). An analysis of a large database of British general medical practices found that the incidence of autism increased sevenfold between 1988 and 1999, whereas the prevalence of MMR vaccination was stable at over 95% throughout the time period (Kaye 2001). A similar analysis in California also found increasing trends in the number of people receiving developmental services for autism during a time when coverage with MMR vaccine was fairly stable (Dales 2001).

An Immunization Safety Review Committee of the Institute of Medicine (Stratton 2001) reviewed the epidemiological and other evidence on MMR vaccine and risk for ASD and concluded that the evidence favors rejection of a causal relationship at the population level.

Other review panels have reached similar conclusions (UK- MRC review 2001; AAP - Halsey 2001). The IOM committee, however, went on to state that it "... could not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children, because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD and the proposed biological models linking MMR vaccine to ASD, although far from established, are nevertheless not disproved." (Stratton 2001)

Wakefield has proposed that autistic enterocolitis is a new clinical syndrome that is associated with MMR vaccination as supported by laboratory evidence of persistent measles virus infection in the intestines of affected children (Wakefield 2000; Uhliman 2002). 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. However, we did not find an association between age at vaccination, most notably by 18 months or 24 months, and autistic regression. The study by Taylor also did not find an increased risk of onset of regression associated with MMR vaccination (Taylor 1999). A recent analysis of a large database of general medical practices in the United Kingdom found that children with autism are no more likely than children without autism to have gastrointestinal disorders requiring medical evaluation (Black 2002). Two separate studies comparing samples of patients from time periods before and after the introduction of MMR vaccine found no evidence for a new variant of MMR-induced autism (Fombonne 2001; Taylor 2001). The proportion of autistic children with regression or with bowel symptoms was not different between the two time periods and there was no association of the co-occurrence of developmental regression and bowel symptoms with MMR vaccination.

In addition to regression, we evaluated other clinical sub-types of ASD, including cases with and without mental retardation, and cases that did not have birth defects 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 cases without mental retardation were more likely to have been vaccinated before 36 months of age than their matched controls. [check correlation between no MR and age 3-5]

In analyses in which we evaluated associations within different subgroups according to demographic factors and birth characteristics, we found no significant associations with vaccination before 18 months or before 24 months in any of the subgroups. The association with vaccination before 36 months was more pronounced in the 3 to 5 year old age group. As mentioned previously, this finding may have been influenced by vaccination requirements for enrollment in early intervention programs.

Although MMR vaccine has received the most attention, other concerns have been raised about vaccinations and autism, especially about thimerosal, the mercury-containing preservative that until recently had been included in multi-dose preparations of certain vaccines (IOM thimerosal 2001). No published data are currently available to address autism risk associated with thimerosal and we were not able to evaluate this exposure. The routinely recommended infant vaccines that used to contain thimerosal are DTP, hepatitis B, and Hib. Neither of these

vaccines, however, were required for school attendance during the period of our study and they were incompletely recorded in the school records. MMR does not contain thimerosal.

In conclusion, we found that the overall distribution of ages at MMR vaccination among children with autism was similar to that of school-matched control children who did not have autism. When we analyzed associations according to different age cut-offs, we found that similar proportions of cases and controls had been vaccinated according to the recommended schedule (i.e., before 18 months of age) or before the usual age of onset of atypical development (i.e., 24 months). No significant associations for either of these age cut-offs were found for specific case subgroups, including regression. Delayed vaccination beyond 36 months was less common among cases than controls, but there were relatively few children in either group with delayed vaccination and this finding may have been influenced by factors related to health care and early intervention program requirements after the manifestation of developmental delays or autistic behaviors.

Acknowledgements

Nancy Doernberg, Catherine Murphy, Catherine Rice

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Table 1 Comparison of demographic characteristics and cognitive level between children included in the MMR study and those that were not include in the study

Characteristic	Children included in the study (N=661)		Children NOT included (N=326)	
	N	%	N	%
Age Group				
3-5 year olds	224	34	121	37
6-10 year olds	437	66	205	63
Child's sex				
Male	531	80	260	80
Female	130	20	66	20
Cognitive level				
No MR	260	39	146	45
MR	401	61	180	55