Frank

Age at First MMR Vaccination and Autism

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DRAFT

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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 subgroups to determine if the more homogenous subgroups were more likely to be associated with the age of MMR vaccine.

Methods

The CDC's Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) was used to identify children with autism (N=647) who met the MADDSP surveillance case definition for autism and had school records available in one of 9 school systems in the 5 county Atlanta surveillance region. Control children (N=1,891) 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. Potential confounding variables were evaluated individually for their impact on the MMR-autism association.

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 increase in prevalence, coupled with reports of increasing numbers of children with autism being served by schools and service agencies (California Department of Developmental Services,1999) have prompted concerns about the role of environmental factors. One of the environmental factors implicated is vaccines particularly the MMR vaccine. The recommended Advisory Committee on Immunization Practices (ACIP) schedule for the MMR vaccine coincides temporally with the age of onset of autism.

Wakefield and colleagues ~~have proposed that MMR vaccine may cause 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 child's parents or pediatrician suggested that MMR vaccine contributed to 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~~

The evidence in support of an association is limited (refs, AAP, IOM) and however

~~initial publication of the Wakefield report, several~~ epidemiologic studies have failed to find 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). These studies, however, have been limited to varying degrees by incomplete case ascertainment, small sample sizes, and reliance on clinical diagnoses without standard case definitions. No studies have been published that included a concurrent comparison or control group with individual-specific vaccination histories.

Will want to add the IOM conclusions here.

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 compare the MMR vaccination histories of a nearly complete population-based sample of children with autism and school-matched controls who did not have autism. We also evaluated associations with MMR vaccination in subgroups of children according to different presentations within the broader category of autism spectrum disorders (ASD).

Methods

Study population Cases

Children with autism were derived from the CDC's 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 five-county metropolitan Atlanta area (Yeargin-Allsopp, M. et al., 2002). ~~MADDSP was established to ascertain all children with one or more of five developmental disabilities -- mental retardation, cerebral palsy, autism, hearing impairment, and vision impairment -- who were 3 to 10 years of age and whose parents resided in the five-county metropolitan Atlanta area.~~

3-10 y.o.

Details of the surveillance system for autism have been published separately. Briefly, . . . (see note top of next page)

Need to give more detail on:
1) Source of cases (schools, providers, etc.)
2) Std. chart review of all available records by trained abstractors
3) Review by autism experts; 4) case defn.

Cases

In the first MADDSP autism prevalence study, they identified 987 confirmed autism cases from 1,077 children who had information available for review from the multiple-source records (Yeargin-Allsopp, M. et al., 2002). For the purpose of this study, we identified 647 confirmed autism cases that also had records available from one of the nine participating school systems used as part of the MADDSP surveillance system. The remaining case children 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 are being home schooled. We searched for school records of case children across all school systems in order to identify their school of enrollment at the time of abstraction.

Controls

We attempted to obtain a 3:1 control to case ratio for this study. For 97% of the cases, we identified 3 controls while the remaining 3 percent of cases had fewer than 3 controls. Control children (N=1,891) 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. However, if a case-child was attending a school that was structured for special education students (e.g., psycho-educational school), controls were selected from the case-child's home school. A child's home school is the school in the child's neighborhood or residential area that the child would attend if the child did not have a disability. 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. The names of control

children were verified in the MADDSP and special education files to assure that they were not receiving special education services **(in 1996 or ever???)**.

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 school record ~~file that is kept at the school where the child is enrolled~~. During the period of this study, Georgia law required at least one dose of measles, mumps, and rubella vaccine in the form of either 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 vaccination exemptions~~ (medical and religious) ~~were also recorded.~~

Family Background Characteristics and Other Data Collection

Demographic information including child's date of birth, gender, birth state, and race/ethnicity was obtained from the birth certificate that is kept in the child's permanent 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, a school registration form was used to obtain the necessary demographic information.

Subsequently, cases and controls born in Georgia were matched to state birth certificate records in order to derive more information on ~~child~~ and maternal characteristics. The matching criteria used were birth certificate number and child's first and last name. Of the children

identified as being born in Georgia, 57% of cases (N=359) and 56% of controls (N=1,049) were successfully matched. Variables obtained from the birth certificate included child ~~factors of~~ birth weight and gestational age and ~~maternal factors of~~ the mother's parity, age, race/ethnicity, and education.

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, level of cognitive functioning, as well as prenatal and perinatal conditions. 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).

MMR Exposure Variable

The primary exposure of interest in the study was age of receipt of the first dose of the MMR vaccine. We examined two alternative exposure periods for age of MMR vaccination: receipt of the MMR vaccine < 18 months of age and < 24 months of age. These exposure periods were chosen because regression occurs at approximately 18 months of age and the 24-month time period is well beyond the median age of first parental concern for autistic features as well as median date for the MMR vaccine (APA, 1994; Giacomo, A. & Fombonne, E., 1998;Taylor, B., 1999). Therefore the period after 24 months would be considered an unexposed period for the causal association between the timing of receipt of the vaccine and autism.

Classification of Autism Subgroups

~~The IOM (2001) specifically recommended additional research regarding the potential susceptibility of certain subgroups of autism~~. 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 to identify additional information that would help classify cases into more homogenous subgroups, particularly children with indication of delay less than one year and children with pre-existing conditions. The information that was collected included age of first parental concern, the presence of a pre-existing condition, date of concern, and verbatim description of the behaviors that led to the concern. A family history of autism and related autism spectrum conditions, and other developmental disabilities was also recorded.

Did we use this?

Indication of developmental delay at less than one year was ~~described~~ 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.

Need to define

Statistical Analyses

Add analysis comparing the overall distributions of age at vaccination.

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. Potential confounding variables were evaluated individually for their association with the autism case definition. Those with an odds ratio p-value < 0.20 were included as covariates in a conditional logistic regression model to estimate adjusted odds ratios for the association between age at vaccination and autism. **(should we describe referent groups and confounders ???)**

We examined two subgroups of autism cases: 1) case children with any pre-existing condition that was identified before the age of 1 year by either a medical provider or the parent and 2) case children with a regression or plateau of developmental milestones described in their records **(????)**. Pre-existing conditions included an established cause for autism, a co-occurring

? add co-existing conditions

group of interest is actually those without pre-existing conditions

condition suggesting an early prenatal etiology (e.g., tuberous sclerosis, fragile X, or other congenital/chromosomal anomalies), parental concern before the age of one, and developmental disability ascertained by MADDSP that were diagnosed before age 1 years.

In the results, I think we should have separate tables for the ASD cases and the sub-categories

Table X : Associations c ASD

Total sample
B.C. sample (unadjusted)
B.C. sample (adjusted)

Table Y : Associations c selected ASD categories

No delay before 1 yr.

Total sample
B.C. (adj./unadj.)

No Co-occurring conditions

Total sample
B.C. (adj./unadj.)

Regression/ Plateau

Total sample
B.C. sample (adj./unadj.)