Methods

Data for the study came from four main sources: 1) CDER data; 2) Regional Center charts; 3) The Autism Diagnostic Interview — Revised (ADI-R)*; and 4) a detailed study questionnaire. Additional sources of information were the Social Communication Questionnaire (SCQ)*, the Checklist for Autism in Toddlers (CHAT), the Regression Validation Interview (adapted from a questionnaire from the Autism Regression/ Vaccination Study), and immunization records provided by either the participating family or a health-care provider. Details of the research methods are presented by each study aim below, followed by a description of recruitment and enrollment procedures.

Methods for Study Aim 1: *Change in diagnostic criteria associated with CDER status 1 autism.*

One possible explanation for the observed increase in number of cases of CDER status 1 autism is that the criteria for determining if a child has full syndrome autism may have changed. To study temporal changes in diagnostic criteria associated with CDER status 1 autism, DSM-IV criteria for autism were assessed in two birth cohorts of children with a diagnosis of full syndrome autism in the Regional Center system. The two birth cohorts were children born between 1983-1985 (Cohort 1) and children born between 1993-1995 (Cohort 2). A random sample of children from these two groups was systematically selected to represent each Regional Center in California. DSM-IV criteria were assessed by 1) reviewing the Regional Center record to determine documentation of diagnostic criteria applied at the time the child received the autism diagnosis; and 2) conducting an ADI-R interview with the parents or guardians of the child with autism. The ADI-R is an instrument that provides a semi-structured interview of parents or care providers of children or adults with suspected pervasive developmental disorders including autism.[36] The ADI-R can be scored to determine whether the child meets DSM-IV criteria for autism. This study instrument also probes for features of autism that may not currently apply to the child, but did occur in the past, allowing for one standard to be applied to children of different ages.

Uncertainty about the increasing prevalence rates of autism raises doubts that genetic factors alone are responsible.

Methods for Study Aim 2: *Proportion of children with DSM-IV autism classified as having mental retardation.*

Another potential explanation for the observed increase in the number of cases of autism is that some children with autism may have been misclassified as having

* Autism Diagnostic Interview-Revised (ADI-R) and Social Communication Questionnaire (SCQ), copyright 2001, Western Psychological Services, Los Angeles, CA. The U.C. Davis M.I.N.D. Institute was provided license and authorization to reprint these instruments for specific research use.

mental retardation, and that more of these misclassifications occurred in the past. The number of children with mental retardation served by the Regional Centers is significantly greater than the number of children with CDER status 1 autism, and a small change in the rate of misclassification of children reported as having mental retardation could effectively double the autism rate.

We investigated whether or not more children who meet autism criteria were misclassified as having mental retardation (without autism) in the past compared to the present.

Two birth cohorts of children determined to have mental retardation without CDER status 1 autism were studied to determine the proportion of these children who meet or have met DSM-IV criteria for autism. As with Study Aim 1, Cohort 1 is comprised of children born between 1983-1985 and Cohort 2 is comprised of children born between 1993-1995. For each participating child, parents or guardians completed a Social Communication Questionnaire (SCQ). The short SCQ (previously named the Autism Screening Questionnaire) can be used to screen for autistic-like behaviors. A positive score indicates that a child may have an autism spectrum disorder, but does not confirm an autism diagnosis. Positive SCQ scores were followed up with a confirmatory ADI-R. As with Study Aim 1, results of the ADI-R have been equated with DSM-IV criteria. It is recognized that DSM-IV criteria is a standard that was not established at the time that many of the children in Cohort 1 were diagnosed with mental retardation, but these criteria are the standard for comparison in this study.

A possible explanation for an observed increase in cases of autism is that children with autism from other states move to California for care.

Methods for Study Aim 3: *Change in in-migration of children with autism that accounts for increased number of cases of CDER status 1 autism.*

A third possible explanation for an observed increase in cases of CDER status 1 autism is that children with autism from other states move to California for care. If there has been a temporal increase in the proportion of children with autism who were born out-of-state and moved to California for developmental or educational services, then there could be an increase in the number of children with autism served by the Regional Center system that is not due to increased autism rates among the children of California. It is not expected that in-migration will account for 100% of the observed increase in cases of autism, but it could account for some portion of the observed increase.

Methods for Study Aim 4: *Change in characteristics of children with CDER status 1 autism over time.*

Some have suggested that the profile of children with autism has changed such that those autistic children who were more recently diagnosed are more likely to have higher cognitive function and to have experienced regression and gastrointestinal symptoms than children diagnosed in the more distant past. The DDS Report suggests that children more recently reported with CDER status 1 autism are less likely to have mental retardation. This finding has not been previously verified. For Study Aim 4, we evaluated the sample of children with CDER status 1 autism constructed for Study Aim 1 to assess any overall changes in demographic and other characteristics over time. Families completed a detailed study questionnaire or were interviewed to determine demographic information, presence of mental retardation, seizures, associated medical conditions, and problems or environmental exposures during the pregnancy. A history of gastrointestinal symptoms or loss of developmental milestones (regression) in the child was also ascertained. A list of questions is provided in Appendix 5.

Some have suggested that the profile of children with autism has changed.

Methods for Study Aim 5: *Determination of what families believe to be the cause of autism in their child and whether this has changed in two age cohorts.*

We asked the question, "What do you think caused your child's autism or other developmental problem?" to parents of children with autism. This question was included as part of the detailed study questionnaire or interview that was used for Study Aim 4. Responses to this question were compared between the two birth cohorts.

Methods for Study Aim 6: *Determination if vaccination with MMR increases the recurrence rate of autism in subsequent (younger) siblings.*

Based on discussions with the California Birth Defects Monitoring Program and the Centers for Disease Control in Atlanta, Georgia, anecdotal reports suggest that many — up to half — of families with one child affected with autism or PDD are opting out of vaccinating subsequent siblings with MMR. The recurrence rate of autism among families with at least one affected sibling is relatively high (approximately 5%), allowing for a "natural experiment" to investigate whether or not the rate of autism in subsequent siblings is higher among those families who elect to have siblings vaccinated with MMR, compared to families with autistic children who choose not to have subsequent siblings vaccinated with MMR.

The recurrence rate of autism among families with at least one affected sibling is relatively high allowing for a "natural experiment" to investigate whether or not the rate of autism in subsequent siblings is higher among those families who elect to have siblings vaccinated with MMR.

This study aim was investigated by including questions about siblings and vaccination choices made by parents with subsequent siblings. These questions were asked of the entire sample selected to answer Study Aims 1, 3, 4 and 5. For the sub-sample of children with autism who have younger siblings, we investigated the association of vaccination choices, specifically MMR and Hepatitis B vaccines, and the development of autism in these siblings. The incidence of autism and PDD among subsequent siblings was ascertained by asking the family to complete either the SCQ for siblings 24 months of age and older, or the CHAT for siblings 18 months of age through 23 months of age. Vaccine exposures (e.g. vaccination with MMR) were gathered by requesting a copy of the siblings' immunization records from the family or health-care provider (if the family did not have a copy). Among families with at least one child affected with autism, assuming an adequate sample, we would compare the rate of autism and/or PDD among vaccinated siblings to the rate among unvaccinated siblings (and to partially vaccinated siblings).

Recruitment and Enrollment Procedures

The CDER records formed the basis for identifying study subjects for this study. In the 1983-85 cohort, the number of children with mental retardation (without CDER status 1 autism) was 12 times greater than that of children with CDER status 1 autism. In the 1993-95 cohort, the MR numbers were only 3-fold that of the autism numbers. These changes reflect a tripling of the number of children with autism between these birth cohorts that are separated by 10 years and reduction by approximately 25% the number of children with mental retardation over this same period.

The target sample was approximately 250 children in each group (AD1, AD2, MR1 and MR2). The sampling frame was constructed to include 6 times the target number, or approximately 1500, in each group, except for the older autism group (AD1) for which there were only 991 children. Within the 4 study groups, target enrollment numbers were determined for each Regional Center based on the proportion of children with each condition (AD and MR) within each age group (Cohort 1 and Cohort 2). Further details of the selection of target sample by Regional Center and sample size calculations can be found in Appendix 6.

The study population was limited to those children whose CDER reports were included in the Regional Centers' administrative data. Families were asked to participate in this study based on a random sample of children who received Regional Center services. Thus, each family that was selected for the study received at least one unsolicited invitation to participate. It was our intention for this study to recruit and enroll families in the least invasive manner possible. "Low Impact" was the term we used to describe our approach to initial and follow-up contact and other study procedures. The specific procedures that we employed to contact and inform families about the study, as well as what families did if they agreed to enroll, are described below.

How we contacted families and obtained informed consent to participate.

As described previously, we had four study groups based on the child's diagnosis in CDER (full syndrome autism or mental retardation without full syndrome autism) and the year of birth (1983-85 and 1993-95). Potential study subjects were separated by cohort and by the Regional Center where they were first assessed and determined to have full syndrome autism (in the case of autism cohorts 1 and 2) or mental retardation (MR cohorts 1 and 2). These groups were then randomly sorted by Regional Center, year of birth, and diagnosis to produce a sampling frame. Recruitment proceeded by mailing a recruitment packet to families according to their position on the randomly ordered list. The packet included a letter from DDS describing the study, a one-page description of the study procedures, informed consent documents, and an anonymous response form and postage paid envelope. All items were printed in both English and Spanish. These packets served as an "introduction" of the UC Davis study staff to the potential study subjects. We conducted one follow-up mailing if we had no response within three weeks of the first mailing.

Participation in the study was voluntary. Families who declined to participate, or who didn't respond, were replaced by the next child on the random list of study subjects based on the age group, diagnosis, and the Regional Center. Families could contact us using a toll-free number or return a response form in a postage-paid envelope. Upon hearing from a family that they were interested in participating we reviewed with them the study procedures.

Chart abstraction

We requested a photocopy of the Regional Center record after receiving the written informed consent (which authorized the release of these records). Photocopies were made either by a contracted company (after the chart was pulled by Regional Center staff) or by Regional Center staff themselves.

Specific procedures for families of children with autism

Scheduling the ADI-R interview

After agreeing to participate in the study, families were scheduled for an ADI-R interview. In most instances, these interviews were conducted at the Regional Center branch office that was closest to the family. A trained, certified staff person administered the ADI-R. The instrument was translated into Spanish for use with Spanish-speaking families. Parents/guardians were paid $35 at the conclusion of the interview to compensate them for their time.

If the family reported a history of regression during the ADI-R interview, a more detailed assessment was conducted by administering the Regression Validation Interview over the telephone with a parent or guardian. The Regression Validation Interview was adapted from a questionnaire developed for the Collaborative Programs of Excellence in Autism (CPEA) Autism Regression/Vaccination Study.

Completing the study questionnaire

A copy of the study questionnaire was mailed to the family for completion upon receipt of the signed consent document. We provided a pre-addressed, postage-paid envelope in which to return the completed questionnaire. If the family requested a telephone interview to complete the study questionnaire this was set up when we received the consent document.

Evaluation of younger siblings

If there were younger half- or full siblings of the autistic subject, we requested that the parent/guardian complete one of two autism-screening tests for each younger sibling, based on the age of the sibling. For younger siblings who were younger than 18 months, we requested permission to contact the family when the child turns 24 months old to assess vaccination status and developmental outcomes.

For siblings at least 18 months of age but less than 24 months of age:

The parents/guardians were asked to complete a Checklist for Autism in Toddlers (CHAT) form for any sibling within this age group. Results were scored using standard documentation and entered into a sibling database.

For siblings at least 24 months of age:

The parents/guardians were asked to complete a SCQ for each sibling 24 months of age or older. Results were scored using standard documentation and entered into a sibling database.

Completion of enrollment

Study staff reviewed the returned questionnaires and contacted families by telephone to clarify inconsistencies or to complete responses that appeared inadvertently omitted. We sent a check in the amount of $30 to the family to thank them for completing the questionnaires.

Specific procedures for families with children with mental retardation

Completing the SCQ and study questionnaire

A copy of the study questionnaire and SCQ were mailed to the family for completion upon receipt of the signed consent document. We provided a pre-addressed, postage-paid envelope in which to return the completed questionnaire. If the family requested a telephone interview to complete these instruments this was set up when we received the consent document. Study staff reviewed returned questionnaires and contacted families by telephone to clarify inconsistencies or to complete responses that appeared inadvertently omitted.

Assessment for autism using the ADI-R

An ADI-R interview was scheduled at the local Regional Center for families of study subjects with mental retardation whose SCQ scores were positive (score ≥ 22).

Completion of enrollment

We sent a check in the amount of $35 to the family to thank them for completing the two questionnaires. If the family participated in an ADI-R interview they were also compensated $35 for their time at the interview.

Validating Study Methods and Procedures

A small study was conducted to test all aspects of the study (identification of children in two age cohorts with autism and children with mental retardation, performance of the ADI-R and SCQ, Regional Center chart abstraction, and conduct of the interview.). This study involved two Regional Centers, Alta California and Valley Mountain, due to their proximity to the M.I.N.D. Institute. The year of birth for subjects selected in the pilot differed from the statewide study, with children born in either 1986 or 1987 (Cohort A) compared to children born in 1991 or 1992 (Cohort B). Letters inviting participation in the study were sent to 100 families of children with autism (50 in each

age cohort) and 100 families of children with mental retardation (50 in each age cohort). Response rates were higher among the autism group, 38% for Cohort A and 44% for Cohort B. Fewer families whose children had mental retardation participated in the pilot, 16% of those in Cohort A and 10% of those in Cohort B. As a result of the low response rate in the MR group, incentives were increased in the statewide study. The test study suggested that there was some degree of discrepancy between the CDER record for autism and ADI-R results. Also, cases of autism were found in the MR group. The sample in the test study was too small to draw any definitive conclusions, but pilot testing demonstrated that five of six of the study aims would likely be answered by the statewide study. The test study sample size was insufficient to answer the last study aim. This study aim was included in the statewide study to provide additional data on vaccination practices in families with children with autism.

Statistical Analysis

Potential research subjects based on diagnostic group, Regional Center, and age cohort as drawn from CDER records were randomly ordered within a "cell." Recruitment proceeded in each cell until the target number was achieved or the random list was exhausted. Analysis with SUDAAN software accounted for this complex sampling strategy by nesting the analysis by Regional Center, age cohort, and condition (AD vs MR).[37] Posthoc analyses used some of the CDER data to adjust for differing response rates within cells.[38] The probability of enrollment by Regional Center, age cohort, and condition, as well as factors recorded in the CDER data that might influence the likelihood of response or enrollment were determined in these enhanced models. For both groups, these models included (1) a dichotomous variable for whether or not an individual had multiple CDER records (assuming that children with longer contact with the Regional Centers might be more inclined to participate), (2) sex, (3) a dichotomous variable for whether or not a child was living at home with their parent(s), (4) a dichotomous variable for a primary language of English, and (5) a dichotomous variable for a primary language of Spanish. For the autism groups, an additional dichotomous variable was included for whether or not a child with a CDER status 1 autism diagnosis subsequently loses that autism designation. For the MR group, an additional variable was included that specified whether or not a child had any CDER record with the designation of an autism spectrum disorder (CDER Status 2, 4, or 9). Weighting factors were determined using the calculated probability of enrollment for each subject who was sent a mailing requesting participation and factoring in the likelihood of mailing within a given cell. P-values were considered statistically significant if they were ≤ 0.05.

Recruitment and Enrollment

Table 1 summarizes the recruitment and enrollment for the study. There were differences in response rates based on the condition and the age group (response rate: AD1=18%, MR1=10%, AD2=24%, MR2 = 15%). There were also differences in response rate by Regional Center (not shown). A small number of respondents were willing to participate, but either failed to return a signed consent form or did so too late to complete the components of the study. About 5% of recruited families responded that they did not want to participate, mostly citing reasons that they were too busy, or they did not want to subject their child to any more tests. Some were already in other studies, some were dealing with acute medical problems, and some cited privacy concerns. One parent noted that her daughter had Rett's Disorder, one responded that seizures were her child's main problem, and two reported that their child did not have autism. About 15% of our mailings were returned marked "bad address." No response was obtained for 63% of those recruited despite two mailings. The proportion of the enrolled to the target enrollment was highest for the younger group with autism (93%) and lowest for the older group with MR (50%).

Table 1. *Status of recruitment and enrollment efforts as of September 30, 2002 for the Autism Epidemiology Study.*

	Birth Year 1983-85		Birth Year 1993-95	
	CDER Autism (AD1)	CDER MR (MR1)	CDER Autism (AD2)	CDER MR (MR2)
Total CDER records	991	12139	3209	9275
Sampling frame	991	1572	1554	1548
Total mailed (recruited):	892	1388	1161	1384
Enrolled	143	124	232	185
Willing, but didn't return consent	3	5	10	8
Willing but returned consent too late	4	7	10	3
Wait listed (willing but Regional Center group full)	0	0	20	7
Willing, but not English- or Spanish-speaking	1	2	3	1
Initially enrolled but later withdrew from study	13	4	9	9
Responded — not willing to enroll	44	76	48	48
Never responded	540	859	717	920
Other				
Deceased, in file, not mailed	11	71	1	46
Deceased, responded or returned	0	2	0	0
Unmatched ID Number, not mailed	4	12	1	2
Residing in another state, in file, not mailed	23	36	23	18
Residing in another state, responded or returned	3	8	8	8
Bad address in file, not mailed	38	64	15	29
Bad address, returned, undeliverable	138	292	101	193
Recruitment packets not mailed	23	1	353	69