Study Aim 4 Results

We analyzed demographic characteristics of children with CDER status 1 autism. We limited the study sample to those children who met DSM-IV criteria for autism based on the results of the ADI-R interview. Characteristics were compared between the two age groups as in previous analyses. We postulated that significant differences in certain demographic characteristics may help explain the observed increase in autism in California. Basic demographic characteristics for children with autism are shown in Table 6. There were no significant differences between the age groups for sex, race, and maternal or paternal education. Patterns of dominant handedness (i.e. right-handed, left-handed, both) were not significantly different between the two age groups (data not shown). About 75% of parents reported their children were right-handed. Just over 7% of the older cohort and nearly 13% of the younger cohort were reported to be ambidextrous.

Table 6. *Demographic characteristics of children with full syndrome autism, by older and younger birth cohorts, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Characteristic	**Percentage**	**Percentage**	**p-value**
Male sex	90.4%	83.7%	0.08
Race/Ethnicity*:			
White	68.3%	78.3%	0.12
African-American	8.9%	7.4%	0.68
Asian/Pacific Islander	19.5%	14.5%	0.40
Native American	3.5%	3.0%	0.82
Hispanic	27.6%	39.0%	0.06
Parent educational level:			
Father with high school diploma or higher	87.0%	77.6%	0.06
Father with college associate's degree or higher	40.3%	38.7%	0.81
Mother with high school diploma or higher	86.5%	89.1%	0.54
Mother with college associate's degree or higher	35.5%	33.3%	0.70

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Parents could select multiple responses for the race/ethnicity question.*

Parents of autistic children did not universally report the diagnosis of "full syndrome" autism. Table 7 shows the diagnoses that the parents reported. A greater proportion of older children were reported to have a diagnosis of Asperger's Disorder. This finding may be due to a shift over time in how high functioning children have been labeled. While most parents reported that their child's autism improved over

time, parents of children in the younger cohort were more likely to do so (results shown in Table 8).

Table 7. *Percentage of children with a diagnosis of autism or other autistic disorders as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Autism Spectrum Diagnosis (multiple responses allowed)	**Percentage**	**Percentage**	**p-value**
Autism or autistic disorder	84.2%	88.6%	0.34
Asperger's disorder	15.4%	1.7%	<0.001
Childhood disintegrative disorder	0.0%	1.1%	0.13
PDD-NOS*	20.9%	14.5%	0.21
Rett's syndrome	0.0%	0.0%	-
Unknown	2.0%	2.9%	0.72

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Pervasive developmental disorder, not otherwise specified*

Table 8. *Improvement in child's autism as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Parent report of improvement in child's autism	**Percentage**	**Percentage**	**p-value**
Child's autism has improved	80.8%	93.3%	0.01
Those who answered "yes, autism improved" noted improvements in these areas:			
Social interactions	83.3%	82.6%	0.90
Language/communication	87.7%	90.9%	0.43
Behavior/interests/activities	75.0%	81.0%	0.30

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

We found that a diagnosis of mental retardation associated with autism had declined significantly between the two birth cohorts. This decline was consistent in the CDER data, in Regional Center documentation, and with what parents reported to us on the study questionnaire. The definition of mental retardation as used in CDER and Regional Center record documentation is the presence of mild mental retardation or below (IQ ≤ 70). For the study questionnaire, parents were asked "Has your child been diagnosed with mental retardation?," and a Yes or No response was required. Table 9 shows these results.

Table 9. *Presence of mental retardation as documented by CDER, Regional Center record, and parental report, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85		Birth Year 1993-95		
Associated mental retardation	**Sample size**	**%**	**Sample size**	**%**	**p-value**
MR documented in CDER record	120	60.5%	193	26.7%	<0.001
MR documented in Regional Center record	119	49.7%	185	22.3%	<0.001
MR reported by parents	100	41.3%	161	20.8%	<0.001

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Parents of the younger group of autistic children were less likely to report that their child was diagnosed with a tic disorder, depression, or obsessive-compulsive disorder. These differences may be age-related, and over time these disorders may develop in the younger group.

Table 10. *Parent-reported conditions associated with autism diagnoses, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Associated Conditions (multiple responses allowed)	**Percentage**	**Percentage**	**p-value**
Epilepsy	14.8%	9.8%	0.27
Cerebral palsy	2.6%	1.4%	0.41
Tic disorder	7.4%	0.6%	0.02
Obsessive-compulsive disorder	20.5%	5.1%	<0.001
Depressive disorder	15.7%	1.1%	<0.001
Bipolar disorder	0.7%	0.6%	0.95

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Most children with autism did not have a family history of autism. Table 11 presents family histories as reported by parents, and compares these histories by birth cohort. The younger group of children with autism was less likely to have a family history of mental retardation.

Table 11. *Family history of autism or other conditions/disorders as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Reported Family History	**Percentage**	**Percentage**	**p-value**
Autism	12.9%	16.3%	0.47
Asperger's disorder	5.7%	4.7%	0.73
PDD-NOS	2.9%	7.3%	0.07
Mental retardation	30.5%	16.2%	0.01
Tic disorder	3.8%	3.3%	0.82
Obsessive-compulsive disorder	9.2%	8.7%	0.89
Depressive disorder	31.3%	27.4%	0.49
Bipolar disorder	10.5%	8.2%	0.53

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

We asked the family to complete questions about the pregnancy if the biological mother was available to answer the questions. The use of medications or other therapies to become pregnant was reported more frequently by the parents of the younger autism cohort. Overall this involved less than 10% of this group. Additional details of these comparisons are shown in Table 12. Serious viral illnesses were reported in 10% to 13% of pregnancies; most were attributed to flu, and they differed little by age group (Table 13). About 15% of mothers reported receiving a vaccination or shot during pregnancy. Again, there were few age group differences. A health-care provider prescribing bed rest during the pregnancy, due to complications such as vaginal bleeding, elevated blood pressure, or pre-term labor, was reported by about 15% of mothers of autistic children in both cohorts (data not shown).

Table 12. *Percentage of mothers reporting use of medical treatments to become pregnant, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
	Percentage	**Percentage**	**p-value**
Mother used any medical treatment to help become pregnant	3.6%	9.7%	0.08
Medical treatments that were used:			
Took medicine to stimulate ovulation	3.6%	7.9%	0.19
Received hormone shots	1.8%	2.7%	0.57
Treatment/surgery for blocked fallopian tubes	0.9%	0.7%	0.87
Artificial insemination	0.0%	2.9%	0.07
In-vitro fertilization	0.0%	4.4%	0.08

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Table 13. *Percentage of mothers reporting events during pregnancy, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Pregnancy event	**Percentage**	**Percentage**	**p-value**
Flu (respiratory illness with fever, body aches)	8.8%	8.3%	0.89
Any shot or vaccination during the pregnancy	15.6%	13.4%	0.11
Any pre-term labor	14.8%	8.6%	0.17
Took medicine to stop the pre-term labor	8.4%	2.5%	0.06
Received medicine to induce or augment uterine contractions	32.7%	34.9%	0.73

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Questions about maternal substance use before and during pregnancy were asked and the results are summarized in Table 14. Most respondents answered the questions about alcohol and cigarette use. Due to the sensitive nature of drug use questions, they were omitted from early questionnaires until an NIH Certificate of Confidentiality was obtained. Maternal alcohol use prior to pregnancy was about 30% for both birth cohorts. A decline in alcohol use after the mother became aware of her pregnancy was reported for both birth cohorts. There were no significant differences in maternal cigarette smoking or drug use between birth cohorts. For drug use, we queried about the use of marijuana, cocaine, methamphetamines, heroin, methanol, PCP/"angel dust," barbiturates, or LSD immediately preceding or during the pregnancy. There were not enough positive responses on any individual item to support additional analyses.

Table 14. *Prenatal exposure to alcohol, cigarettes, and street drugs by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	**Birth Year 1993-95 (N=161)**	
	Percentage	**Percentage**	**p-value**
Had any alcoholic beverages ≤ 12 months before child was born	34.7%	29.2%	0.39
	Ave # drinks/mo.	**Ave # drinks/mo.**	
Average number of drinks per month before learned of pregnancy	2.74	2.45	0.79
	Percentage	**Percentage**	
Had any alcoholic beverages after learned of pregnancy and before child was born	3.0%	5.4%	0.28%
	Ave # drinks/mo.	**Ave # drinks/mo.**	
Average number of drinks per month after learned of pregnancy and before child was born	0.18	0.37	0.39
	Percentage	**Percentage**	
Had any cigarettes ≤ 12 months before child was born	14.5%	9.7%	0.26
Had any cigarettes after learning of pregnancy and before child born	10.3%	6.4%	0.28
Used any street drugs ≤ 12 months before child was born	10.2%	6.3%	0.37
Used any street drugs after learning of pregnancy and before child born	7.4%	6.5%	0.83

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Virtually all children with autism received at least one vaccination and this did not differ across birth cohorts (98.4% vs. 99.4%, p=.49). There was, however, a substantial difference in families' decisions to avoid or delay at least one vaccination among the older cohort as compared with the younger cohort (7.9% vs. 21.5%, p<.001). As expected, the older group was more likely to have any younger siblings (56.7% vs. 44.8%, p=.07). For families with younger siblings, parents of children in the younger

cohort were more likely to avoid or delay at least one vaccination for a younger sibling (9.5% vs. 20.7%, p=.06).

We asked questions about the presence of specific gastrointestinal (GI) symptoms at various ages. Results of birth cohort comparisons are shown in Table 15. Reported GI symptoms were more common among the younger cohort, especially constipation in the first year, when solid foods were introduced, and when the child was making the transition to table foods. Vomiting was also more commonly reported in the younger cohort during this time period. No differences between age cohorts were noted beyond 15 months of age.

Table 15. *Percentage of children with a history of gastrointestinal symptoms as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	**Birth Year 1993-95 (N=161)**	
	Percentage	**Percentage**	**p-value**
No gastrointestinal problems in the newborn period	59.7%	52.1%	0.24
Percentage of specific gastrointestinal problems during the newborn period:			
Constipation	13.5%	21.8%	0.08
Diarrhea	14.0%	12.5%	0.73
Vomiting or reflux	10.9%	20.1%	0.03
Other*	7.1%	5.5%	0.67
No gastrointestinal problems when introduced solid foods	71.2%	59.5%	0.047
Percentage of specific gastrointestinal problems when introduced solid foods:			
Constipation	8.1%	17.9%	0.01
Diarrhea	7.0%	11.8%	0.12
Vomiting or reflux	4.0%	9.5%	0.06
Other*	3.3%	2.3%	0.72
No gastrointestinal problems when transitioned to table foods	73.7%	59.3%	0.01
Percentage of specific gastrointestinal problems when transitioned to table foods:			
Constipation	6.4%	19.1%	<0.001
Diarrhea	10.4%	15.5%	0.21
Vomiting or reflux	1.6%	5.6%	0.05
Other*	3.4%	5.2%	0.47
No gastrointestinal problems from age 15 months to the present	59.6%	58.0%	0.81
Percentage of specific gastrointestinal problems at or after age 15 months:			
Constipation	19.3%	24.0%	0.36
Diarrhea	10.7%	14.0%	0.42
Vomiting or reflux	5.5%	6.7%	0.70
Abdominal pain or cramping	6.8%	7.9%	0.72

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.
**Includes gas, bloody diarrhea, problems swallowing, colic.*

We asked the parents if their child had any food allergies, and if yes, to what food is the child allergic. Results are shown in Table 16. Overall, about a quarter of the parents in both cohorts reported food allergies. Allergies to milk or dairy products were most common, although not significantly different between the two age groups. Reported wheat allergies had increased significantly in the younger age group (3.8% vs. 11.5%).

Table 16. *Percentage of children with a history of food allergies as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Reported Food Allergies	**Percentage**	**Percentage**	**p-value**
Any food allergies	23.8%	25.1%	0.81
Milk or dairy	15.6%	19.3%	0.45
Wheat	3.8%	11.5%	0.01
Eggs	0.9%	3.5%	0.09
Nuts (peanuts, walnuts, etc.)	4.0%	3.3%	0.76
Fruit or berries	1.9%	2.8%	0.60
Vegetables (including tomatoes)	0.0%	1.8%	0.07
Shellfish (shrimp, crab, etc.)	2.2%	1.1%	0.44

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Regression on developmental milestones was assessed by several methods: the inclusion of a series of questions on the study questionnaire, evaluating regression questions from the ADI-R, and administering a follow-up questionnaire for children whose ADI-R indicated regression. More than half of the parents from each birth cohort reported on the study questionnaire that their child had undergone regression. We clarified some of these statements through follow-up phone calls or the additional questionnaire. Many parents were confusing delay in the acquisition of a milestone with regression of a milestone that had been achieved. The distinction between these two developmental issues was made clear during the ADI-R interview, thus the reports of regression from the ADI-R were consistently less frequent (approximately 30%). Nonetheless, both results from the study questionnaire and ADI-R interview show that there were no differences based on birth cohort on the proportion of parents reporting a history of regression in their autistic child.

We followed up reports of regression from the ADI-R by administering a more detailed interview with the parent. These interviews were conducted over the telephone and lasted about thirty minutes. The results of these interviews are summarized in Table 16. Most parents reported that the onset of regression occurred before 36 months of age (75% vs. 80%, p=.86) For those children with regression prior to 36 months, most parents (>75%) reported that their child stopped using words for at least one month. We asked the parents to report the number of words the child was using before this loss of words. The average number of words used prior to regression was

higher for the younger cohort (7.8 vs. 10.9). In summary, the rate of regression of developmental milestones observed in this study is similar to previous published reports (approximately 30% using the ADI-R) and this rate differed little between the two birth cohorts.

Table 17. *Regression of developmental milestones as reported by parents, by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=103)	Birth Year 1993-95 (N=174)	
Evaluation of Regression	**Percentage**	**Percentage**	**p-value**
Regression reported on study questionnaire	60.2%	53.7%	0.31
Regression reported on ADI-R	27.8%	33.6%	0.28
Total number with regression on ADI-R	33	63	
Total number with follow-up questionnaire results	20	45	
Percentage with reported regression by 36 months of age	71.0%	81.9%	0.35
Stopped using words for at least one month	69.1%	70.2%	0.93
Mean total number of words prior to regression (mean +/– SE)	7.8±0.75	10.9±0.93	0.01

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Study Aim 5 Results

We asked the parents, "What do you think caused your child's autism and/or other developmental problem?" We provided a large blank area for parents to write in their response. These were then reviewed and categorized. The responses from parents of children with CDER status 1 autism who met DSM-IV criteria are shown in Table 17. We included those that represented at least 1% of parental responses within either birth cohort and we compared responses between birth cohorts. The most frequent response was "don't know" or leaving that part of the questionnaire blank. The frequency of this response did not differ between birth cohorts. The next most frequent response category was immunizations, with 18.3% of older cohort parents and 33.0% of the younger cohort parents attributing their child's autism to immunizations. Analysis of data from the ADI-R interview showed that parents who reported regression of developmental milestones were much more likely to attribute their child's autism to immunizations (30.5% vs. 49.8% in cohorts 1 and 2 respectively). Genetics was next most frequently cited by parents of children with autism (30.6% vs. 26.6%). Pregnancy related events, birth trauma, and environmental exposures were also mentioned as causes for autism.

Table 18. *Parent responses to question, "What do you think caused your child's autism and/or other developmental problem?" by older and younger birth cohorts, children with full syndrome autism, Autism Epidemiology Study.*

	Birth Year 1983-85 (N=100)	Birth Year 1993-95 (N=161)	
Parent Responses	**Percentage**	**Percentage**	**p-value**
"Don't know" or no response	45.7%	47.9%	0.74
Genetics	30.6%	26.6%	0.49
Pregnancy Related	24.1%	16.3%	0.16
Immunizations (all responses):	18.3%	33.0%	0.005
Immunizations in general	14.9%	26.5%	0.02
DTaP or DTP	4.7%	1.1%	0.10
MMR	1.1%	6.5%	0.005
Birth Events (Adverse)	13.5%	14.6%	0.80
Environmental Exposure	10.0%	12.1%	0.59
Drug Use – Illegal	5.9%	2.7%	0.31
Emotional Trauma	3.5%	3.0%	0.81
Mercury Poisoning	3.3%	3.9%	0.86
Brain Abnormalities	2.7%	1.2%	0.48
Head Trauma	2.7%	1.3%	0.60
Allergies	2.3%	5.4%	0.14
Syndromes (e.g. Fragile X)	2.3%	1.1%	0.41
Virus	2.0%	1.1%	0.57
Ear Infections	1.8%	2.9%	0.49
Drug Use – Over the counter or prescription	1.4%	2.4%	0.51
Antibiotics	1.3%	3.5%	0.18
Gastrointestinal Disorders	0.6%	2.4%	0.16
Nutrition	0.0%	2.9%	0.02
Traumatic Surgery	0.0%	1.8%	0.06
High Fever	0.0%	1.1%	0.13

Study sample was limited to those children who met DSM-IV criteria for autism based on the ADI-R interview. All percentages are weighted and adjusted for the study's sampling design.

Study Aim 6 Results

To assess the association between immunizations and the development of autism, we designed part of this study to make use of potential "natural experiment." It has been anecdotally reported that a significant number of families with autistic children is avoiding or delaying some or all vaccinations in younger siblings. Recurrence of autism within families is more common than in the general population, but still is relatively low (2%-10%). Assuming a recurrence rate of 5%, about 1 in 20 younger siblings would be diagnosed with autism. We postulated that if vaccinations contribute to the development of autism, there should be an observable difference in the proportion of siblings with autism when comparing vaccinated siblings with unvaccinated siblings.

Avoidance of at least one vaccine in younger siblings was reported by 10% of the older cohort and 21% of the younger cohort.

In this study, about half of the children with autism had any younger siblings at the time they were enrolled to participate. Avoidance of at least one vaccine in younger siblings was reported by 10% of the older cohort and 21% of the younger cohort. However, the total number of vaccine-avoidant younger siblings in both birth cohorts was only 19, which is insufficient to answer the question posed in this study aim. Based on our findings of 1) the proportion of families with an autistic child that have subsequent children, and 2) the proportion of families who are avoiding or delaying vaccination in younger siblings, we calculated that we would need a sample size of 7,000 families to properly answer this question.