

1st Draft 1/21/2004

Age at First Measles-Mumps-Rubella Vaccination in Children with Autism and School-Matched Control Subjects

William W. Thompson, PhD

**Presented at the Institute of Medicine Meeting
February 9th, 2004**

Some results that were presented to Walt + Melinda
in 10/2002

CDC Collaborators

Frank DeStefano, MD, MPH

Tanya Karapurkar, MPH

Marshalyn Yeargin-Allsopp, MD

Dr. Coleen Boyle, PhD

Background

Two main arguments that have been proposed in support of association between MMR and autism

1. Prevalence of autism has been increasing at same time that childhood vaccination coverage has increased
2. Temporal association between age at recognition of autism and MMR vaccination

Background - Institute of Medicine, 2001

- IOM rejected causal relationship at the population level between MMR vaccine and ASD
 - Consistent body of evidence showing no association
 - Original case series was uninformative regarding causality
 - Biologic models linking MMR with ASD have been fragmentary
 - No animal models linking MMR vaccine and ASD
- IOM strongly encouraged additional studies to examine possible associations between MMR and subgroups with autism

Study Objectives

Primary objective

- To evaluate the association between autism and age of receipt of the MMR vaccine

Secondary objectives

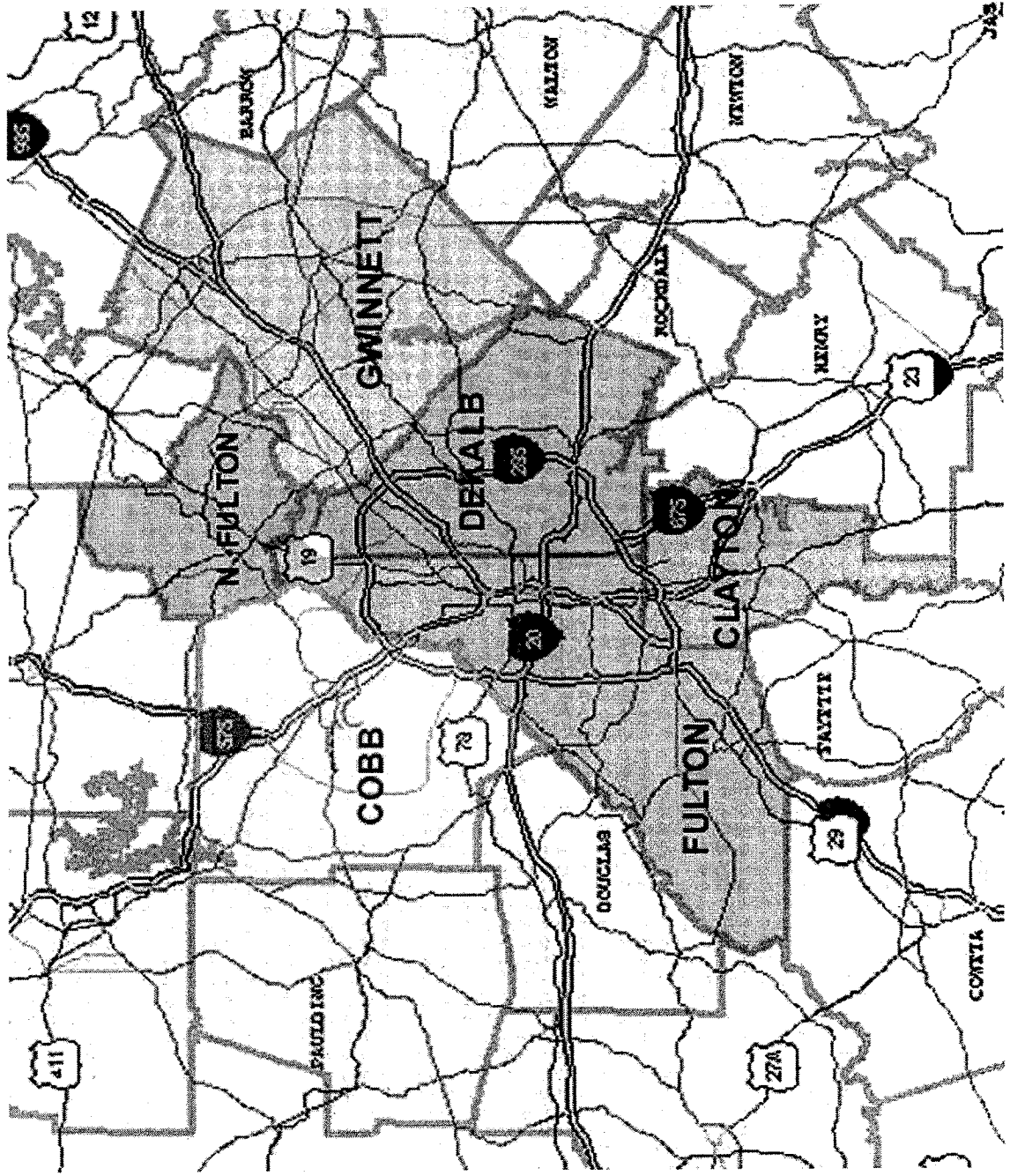
- To compare MMR vaccination histories among certain autism subgroups and controls

Methods - Study Population

- **Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)**

- Population based surveillance program started in 1991
- 300,000 children aged 3-10 years in five county Metropolitan Atlanta area

MADDSP Study Area



Methods - Study Population

- **Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)**

- Multiple source ascertainment of certain developmental disabilities including mental retardation, cerebral palsy, and hearing impairment.
- In 1996, autism was added to the list of conditions monitored in the surveillance system

Methods - Study Design

- **Case-control study design**
 - **Cases: 624 children with ASD**
 - **Controls: 1,824 children without known DDs**

Methods – Selection of Cases

- **Cases: 624 children with ASD**
 - Identified through MADDSP Autism Surveillance in 1996
 - Case children were born between 1986 and 1993
 - Case definition for autism based on DSM-IV criteria from record review with expert review
 - Inclusion in study sample required one of following:
 - Valid MMR vaccination date from school immunization form
 - DTP vaccination by age 2 from school immunization form
 - Immunization exemption form

Clinical Characteristics for Autism Cases (N=624)

Clinical characteristics	N	Percent
Mental retardation	378	61%
Other DD	95	29%
Birth defects	31	5%
Pre-existing condition	235	38%
Regression/Plateau	80	13%

Describe in more detail

Methods – Selection of Controls

- **Controls: 1,824 children without known DD**
 - 3:1 control to case ratio
 - Controls were selected from regular education programs
 - Matched to case-children based on age, sex, and school of attendance at the time of abstraction *
 - Inclusion in study sample required one of following:
 - Valid MMR vaccination date from school immunization form
 - DTP vaccination by age 2 from school immunization form
 - Immunization exemption form

* Certain exceptions had to be made for some ~~case~~ children

OS/1/2007

Methods - Data Collection ????

MADDSP (CDC's Atlanta DD Surveillance System)

MACDP (CDC's Atlanta Birth Defects Program)

School Records

Georgia Birth Certificate Records

Methods - Classification of Autism Subgroups

- **Demographic child and maternal factors:**
 - Gender, age at ascertainment
 - Birth weight, maternal age, education
- **Clinical presentation**
 - Pre-existing condition < 1 year (Yes/No)
 - Regression or plateau (Yes/No)
 - Mental retardation (Yes/No)

Methods - Exposure Variables

*From
take
off*

- **Distribution of Age at MMR Vaccination**
- **Also selected three specific age cut-offs**
 - 18 months: indicator of “on-time” vaccination and also median age for the occurrence of regression
 - 24 months: the upper age limit at which onset of regression or parental concern usually occurs
 - 36 months: the age by which autistic characteristics must have developed according to DSM-IV criteria for autism

Methods - Confounding Variables

Child Background Factors:

- Child's sex
- Child's race
- Birth weight
- Multiplicity

Maternal Background Factors:

- Maternal age
- Maternal education
- Parity

Methods - Analytic Approach

- Conditional logistic regression analysis stratified by matched case-control sets
- Unadjusted Analyses with Total Sample
- Analyses Adjusted for confounding with Birth Certificate Sample

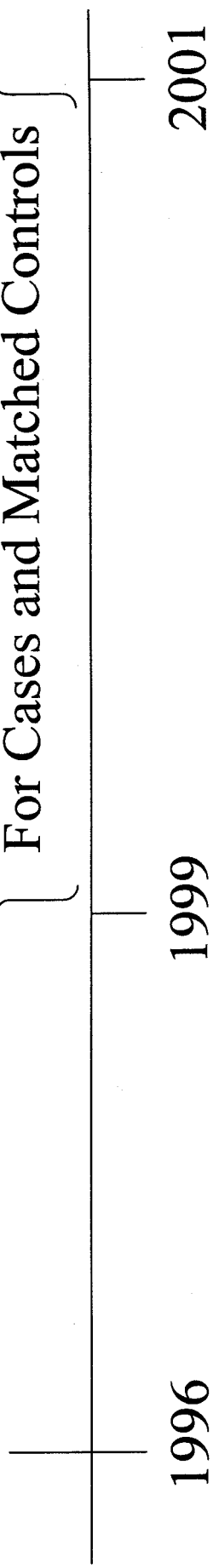
MMR/Autism Case-Control Selection

- MADDSP autism cases were abstracted for a prevalence study in 1996
 - All cases were living in Atlanta metro area in 1996
- Immunization records were abstracted for cases and controls between 1999 and 2001
 - All cases were living in Atlanta at time of immunization record abstraction
 - Matched controls were selected at the time the autism cases had their immunization records abstracted

Case-Control Selection

MADSPP Case
Abstraction

{
Immunization Record Abstraction
For Cases and Matched Controls
}



Sample Characteristics of Children with and without Birth Certificates

	Birth Certificate Sample	No Birth Certificate Sample
Age in 1998	8.2 years	8.6 years
Age at 1 st MMR Vaccination	19.1 months	21.4 months

Sample Characteristics of Children with and without Birth Certificates

	Birth Certificate Cases	No Birth Certificate Cases
Age in 1998	8.3 years	8.5 years
Age at 1 st MMR Vaccination	19.0 months	19.0 months

Sample Characteristics of Children with and without Birth Certificates

	Birth Certificate Controls	No Birth Certificate Controls
Age in 1998	8.2 years	8.6 years
Age at 1 st MMR Vaccination	19.1 months	22.2 months

Results

Table 2: Characteristics of Cases and Controls Both for Total Sample and Birth Certificate Sample

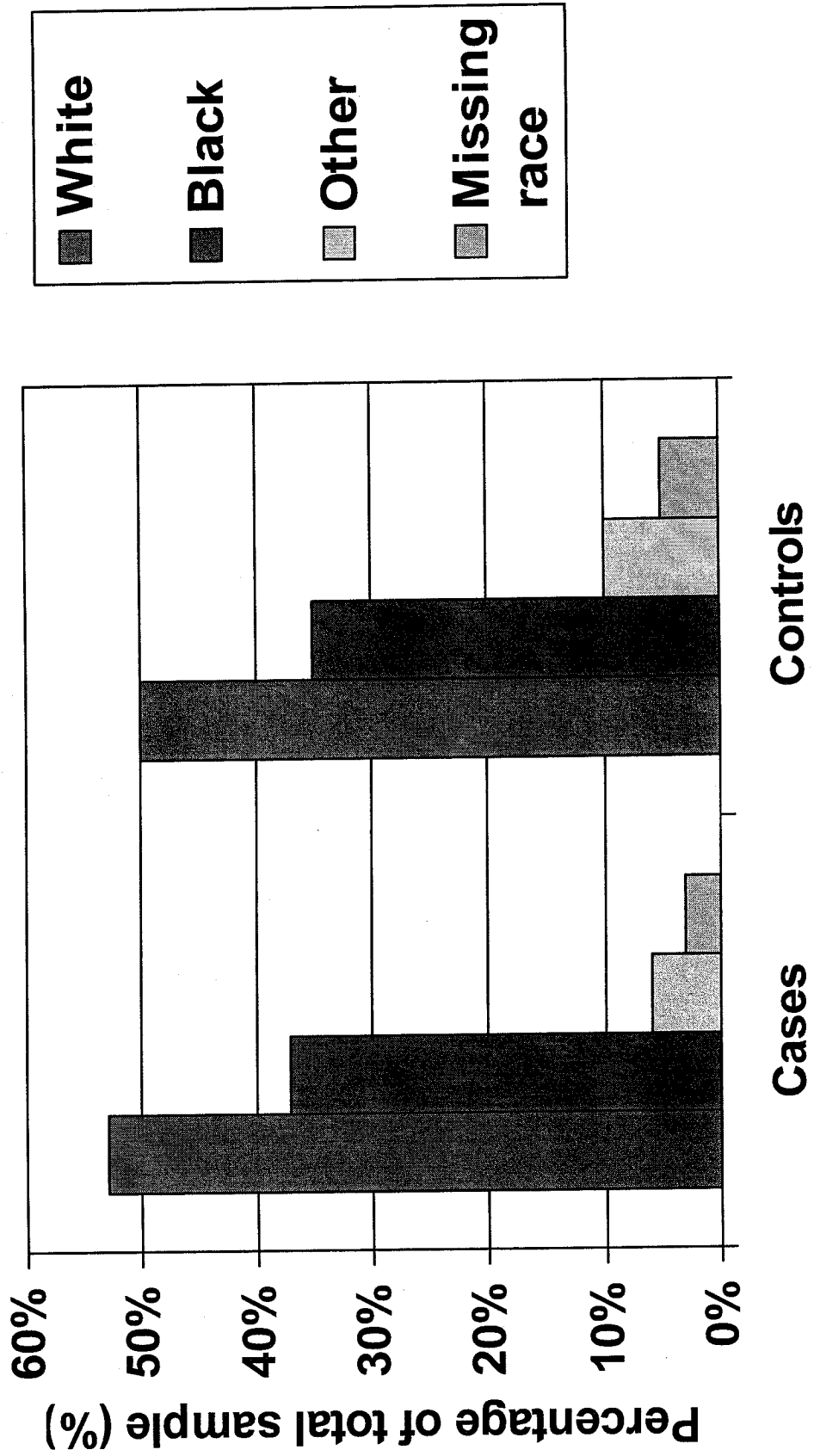
Variable	Category	Total Sample				Birth Certificate Sample			
		Controls		Cases		Controls		Cases	
		N	Percent	N	Percent	N	Percent	N	Percent
Age in 1996	3 - 5 yrs	623	34%	214	34%	376	37%	127	36%
	6 - 10 yrs	1201	66%	410	66%	644	63%	228	64%
Sex	Male	1462	80%	500	80%	809	79%	282	79%
	Female	362	20%	124	20%	211	21%	73	21%
Race	White	918	50%	333	53%	571	56%	199	56%
	Black	636	35%	230	37%	384	38%	137	39%
	Other	174	10%	40	6%	65	6%	19	5%
	Missing	96	5%	21	3%	0	0%	0	0%
Maternal Age	< 20 yrs					95	9%	15	4%
	20 - 34 yrs					803	79%	280	79%
	35+ yrs					122	12%	60	17%
Maternal Educ	<= 12 yrs					466	46%	135	38%
	13 - 15 yrs					253	25%	100	28%
	16+ yrs					301	30%	120	34%
Birth Weight	0 - 1499 gms					11	1%	12	3%
	1500 - 2499 gms					52	5%	37	10%
	2500 + gms					957	94%	306	86%
Multiplicity	Singleton					990	97%	329	93%
	Twin +					30	3%	26	7%
Parity	1st Born					452	44%	149	42%
	2nd or Higher					560	55%	204	57%
	Missing					8	1%	2	1%
Total		1824	100%	624	100%	1020	100%	355	100%

* All subjects reported in this table either received an MMR vaccine or had a DTP vaccine by the age of 2

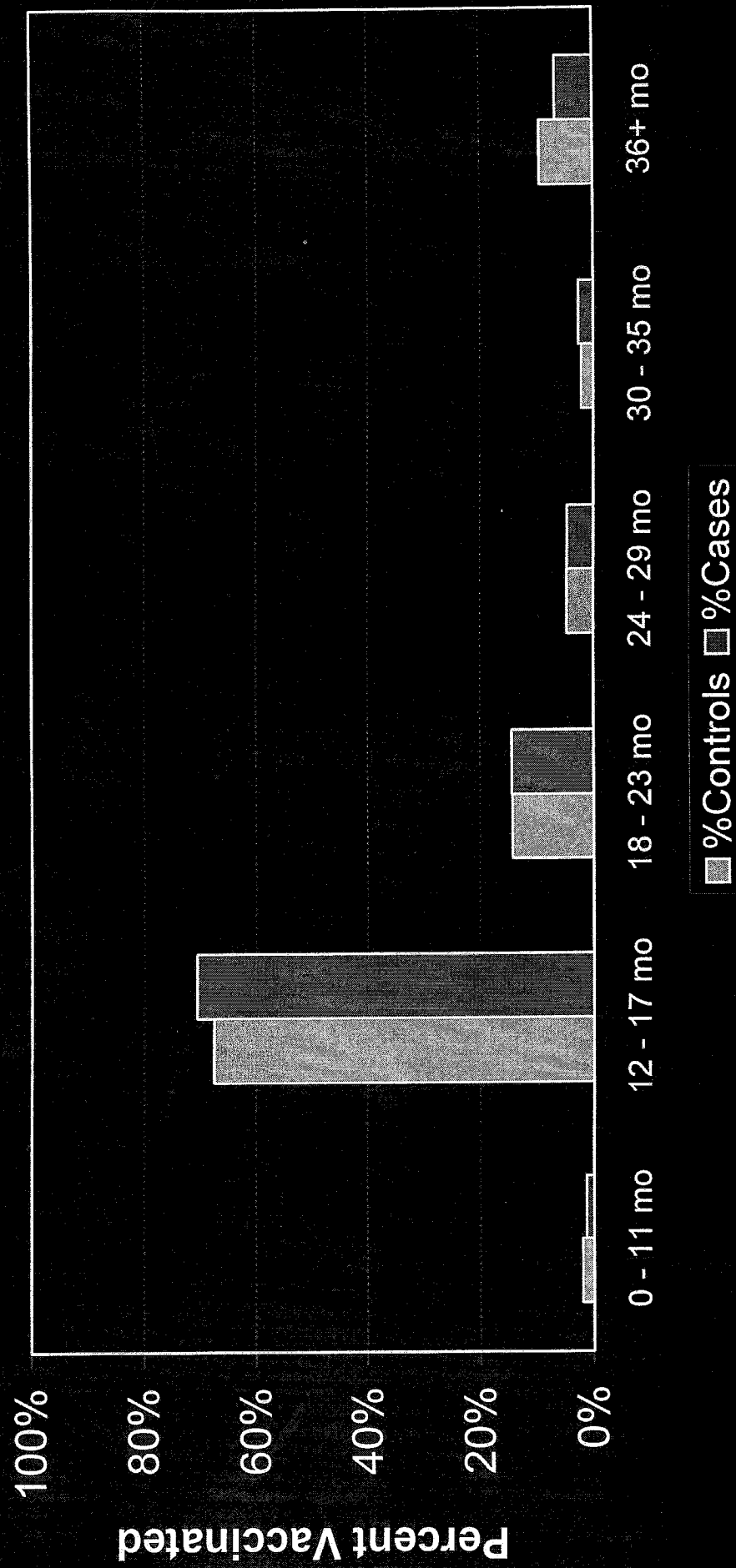
** All cases are confirmed cases

*** The birth certificate sample presented in this table is the unmatched sample.

Racial Distribution of Cases and Controls



Age at 1st MMR Vaccination For Total Sample



Age Cut-Offs for MMR Vaccination

Vaccination Cut-Point	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Vaccinated < 18 Months	1.12 (0.91 - 1.38)	0.93 (0.66 - 1.30)
Vaccinated < 24 Months	1.21 (0.93 - 1.57)	0.99 (0.63 - 1.55)
Vaccinated < 36 Months	1.49 (1.04 - 2.14)	1.23 (0.64 - 2.36)

Demographic Subgroups Children Vaccinated < 18 months

Subgroup	Total Sample OR (95% CI)	Birth Certificate Sample AOR (95% CI)
Males (N=500)	1.22 (0.97, 1.54)	0.94 (0.65, 1.39)
Females (N=124)	0.83 (0.52, 1.30)	0.79 (0.33, 1.86)
3-5 years of age (N=214)	1.08 (0.73, 1.60)	0.77 (0.39, 1.50)
6-10 years of age (N=410)	1.14 (0.90, 1.46)	0.98 (0.65, 1.47)
White/Other+ (N=218)	0.87 (0.59, 1.27)	--
Black + (N=137)	0.79 (0.52, 1.20)	--

Demographic Subgroups Children Vaccinated < 36 months

Subgroup	Total Sample OR (95% CI)	Birth Certificate Sample AOR (95% CI)
Males (N=500)	1.67 (1.10, 2.53)	1.23 (0.64, 2.36)
Females (N=124)	1.06 (0.51, 2.20)	0.24 (0.04, 1.47)
3-5 years of age (N=214)	2.34 (0.99, 5.54)	2.63 (0.51, 13.45)
6-10 years of age (N=410)	1.33 (0.89, 1.98)	1.09 (0.53, 2.30)
White/Other+ (N=218)	0.89 (0.41, 1.94)	--
Black + (N=137)	1.60 (0.78, 3.26)	--

Clinical Case Subgroup Analyses Children Vaccinated < 18 months

Subgroup	Total Sample	Birth Certificate
	OR (95% CI)	Sample AOR (95% CI)
No Pre-existing condition (N=390)	1.07 (0.78,2.41)	1.05 (0.68,1.61)
Regression or plateau (N=80)	1.37 (0.78,2.41)	0.83 (0.23,3.09)
With MR (N=376)	1.06 (0.82,1.38)	1.13 (0.72,1.79)
Without MR (N=248)	1.23 (0.87, 1.73)	0.68 (0.40,1.16)

Clinical Case Subgroups Analyses Children Vaccinated < 36 months

Subgroup	Total Sample OR (95% CI)	Birth Certificate Sample AOR (95% CI)
No Pre-existing condition (N=390)	1.51 (0.96, 2.37)	1.82 (0.77, 4.31)
Regression or plateau (N=80)	1.45 (0.54, 3.93)	0.69 (0.14, 3.30)
With MR (N=376)	1.21 (0.79, 1.84)	0.82 (0.38, 1.79)
Without MR (N=248)	2.45 (1.20, 5.00)*	3.55 (0.74, 17.07)*

* The large OR for the cases without MR was based on only 3 cases that were vaccinated late

Summary of Study Findings

- The overall distribution of ages at MMR vaccination among children with autism was similar to that of controls
- No significant associations were found between vaccination at < 18 or < 24 months and autism or any autism subgroups.
 - No increased risk of autism associated with vaccination by recommended age (18 months)
 - No association with vaccination by 24 months of age when developmental change is noted in most children

Summary of Study Findings

- Cases more likely than controls to be vaccinated < 36 months of age.
 - Case-children more likely to be in contact with health care system, thus, more likely to have “early” vaccinations
 - Case-children more likely be vaccinated as requirement for entry into early intervention special education programs

Study Strengths

- Large population-based sample of children
- Review of clinical information by autism experts
- Data was available regarding exposure and outcome prior to publicity
- Linkage with birth certificate files
- Evaluation of autism subgroups

Study Limitations

- Incomplete information for determining age of onset for autism
- Very small unexposed group
 - most children receive the MMR vaccine by 36 months
- MMR immunization records not available on all children
- Information on potential confounders only available for birth certificate sample

Study Conclusions

- Similar overall distribution of ages at MMR vaccination among cases and controls
- Similar proportions of cases and controls vaccinated according to ACIP schedule (18 months)
- Similar proportions of cases and controls vaccinated by typical age of onset for autism (< 24 months).
- “Late” vaccination less common among cases compared to matched controls (<36 months)