1/29/04

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

William W. Thompson, PhD

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Immunization Safety Review Committee
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Potential Conflicts of Interest

- Full-time employee with Merck & Co from 1996-1998
  - Marketing Department
  - Merck has never provided financial support for any scientific study that I have been involved in
  - Merck employees have never coauthored a scientific study with me
- CDC employee from 1998-Present
  - Influenza Impact and Effectiveness Studies
    - Wyeth-Lederle provided vaccine for one double-blinded randomized placebo-controlled vaccine effectiveness study
    - Quidel Corporation provided influenza rapid tests for an ongoing influenza impact study
  - Pneumoccocal Effectiveness Studies
- I do not own any pharmaceutical stocks

CDC Collaborators

- National Immunization Program
  - Frank DeStefano, MD, MPH
- National Center for Birth Defects and Developmental Disabilities
  - Tanya Karapurkar, MPH
  - Marshalyn Yeargin-Allsopp, MD
  - Coleen Boyle, PhD

Background

- Observations which may suggest a potential association between MMR vaccination and autism
  1. Prevalence of autism has increased at same time that coverage for MMR vaccinations has increased among young children
  2. Timing of initial recognition of autism symptoms occurs about the same time as recommended age for first MMR vaccination
  3. Wakefield et al., (1998) Case Series

Background
Institute of Medicine Review (2001)

- IOM rejected causal relationship at the population level between MMR vaccination and Autism Spectrum Disorder (ASD)
  - Consistent body of evidence showing no association
  - Fragmentary biologic models
  - No well defined animal models
  - Original case series was uninformative regarding causality
- IOM strongly encouraged additional studies to examine possible associations between MMR vaccination and ASD subgroups

Study Objectives

Primary Objective

- Evaluate association between ASD and age of receipt of MMR vaccine
  - Data collection started in 1998

Study Objectives

Secondary Objective

- Compare MMR vaccination histories among ASD subgroups and matched controls
  - Developed in response to IOM (2001) report
  - Data collection in schools was near completion for this study by the time the report was published

Methods - Study Population

- **Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)**
  - Population based surveillance program started in 1991
  - Population area included approximately 300,000 children aged 3-10 years in the five county Metropolitan Atlanta area

Methods - Study Population

- MADDSP Cont.
  - Multiple source ascertainment of several developmental disabilities
    - Mental retardation
    - Cerebral palsy
    - Hearing loss
    - Visual impairment
  - ASD was added to list of conditions in 1996

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**
  - Children born between 1986 and 1993
  - Identified through MADDSP with evaluations available up through 1996
  - Abstraction of records by trained abstractors
  - DSM-IV criteria used to classify children
  - ASD classification determined by ASD experts
  - 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

Methods
Defining ASD Subgroups

- **Pre-existing conditions <1 Year of Age**
  - Any known birth defect
  - Other co-occurring developmental disabilities
  - Major perinatal or postnatal insult that could have contributed to developmental delay
    - CNS Infections
    - Traumatic Brain Injuries

Methods
Defining ASD Subgroups

- Developmental Delay <1 Year of Age
  - Lack of speech at appropriate ages
    - Cooing
    - Babbling
  - Socially unresponsive in 1st year of life
    - Cuddling
    - Appropriate eye contact
    - Responding to parents voices

Methods
Defining ASD Subgroups

- Regression and/or Plateau
  - Children with an indication of loss of age appropriate developmental skills (regression)
  - Children with appropriate skills that failed to progress (plateau)

Methods
Summary of ASD Subgroups

Clinical Characteristics	N	Percent
Mental retardation (MADDSP case def)	378	61%
Pre-existing conditions	235	38%
Regression and/or Plateau	80	13%

- ASD subgroups were not mutually exclusive
- MR definition was IQ < 70

Methods
Selection of Matched Controls

- Controls: 1,824 children without known DD
  - Controls selected at 3:1 ratio
  - Controls selected from regular education programs
  - Matched 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

* Controls for case children in special education schools were selected from the public school the case child would attend as a regular education student

Methods
GA State Birth Certificate Sample

- Matched cases and controls to GA State Birth Certificates to assess effects of potential confounders
  - Maternal Age
  - Maternal Education
  - Child Birth Weight
  - Multiplicity (Singleton versus other)
  - Parity (1st born versus other)
- Results in similar follow-up time for both cases and controls

Methods
Demographic Subgroups

- Demographic Factors From Total Sample
  - Age
  - Gender
- Data from Birth Certificates
  - Race
  - Birth Weight
  - Maternal Age
  - Maternal Education

Methods
Specific Hypotheses

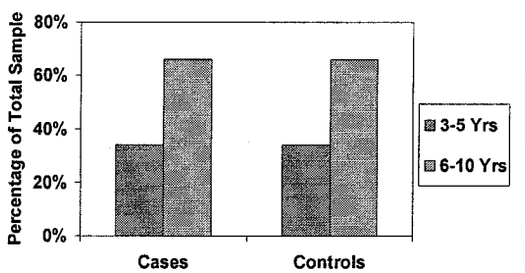
- Assessed whether variation in age at first MMR vaccination was different for cases and controls
- Also assessed 3 specific age cut-offs:
  1) <18 months - evaluation of whether vaccination by the recommended age for MMR vaccination
  2) <24 months – evaluation of whether vaccination by the typical time of first parental concern
  3) <36 months – evaluation of whether vaccination prior to timeframe required by DSM-IV for symptom onset for autism

Methods
Analytic Approach

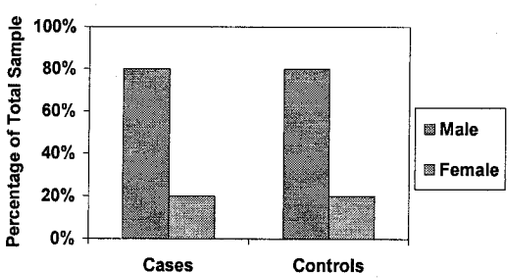
- We used conditional logistic regression analysis stratified by matched case-control sets
- Analyses with Total Sample
  - Unadjusted analyses
  - Subjects did not require a GA State birth certificate
- Analyses with GA State Birth Certificate Sample
  - Unadjusted analyses (not reported in manuscript)
  - Adjusted analyses for confounding with data available from the birth certificate

Descriptive Data

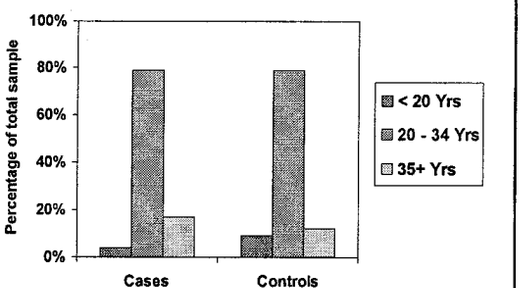
Descriptive Data
Age Distribution of Cases and Controls



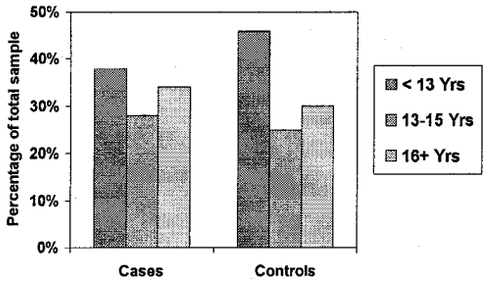
Descriptive Data
Sex Distribution of Cases and Controls



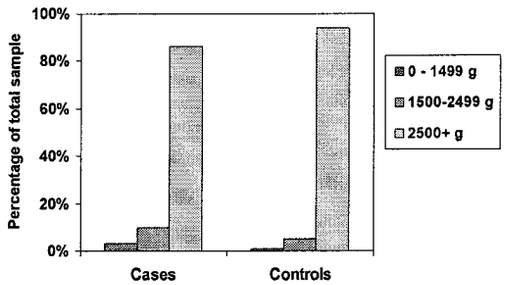
Descriptive Data
Maternal Age from Birth Certificate



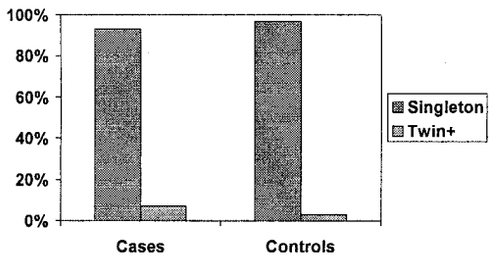
Descriptive Data
Maternal Education from Birth Certificate



Descriptive Data
Birth Weight from Birth Certificate

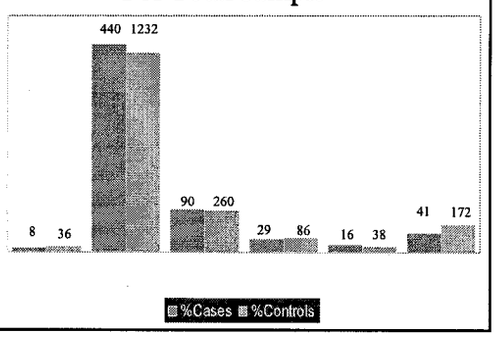


Descriptive Data
Multiplicity from Birth Certificate



Results

Age at 1st MMR Vaccination
For Total Sample



Demographic Case Subgroup Analyses
For Total Sample

Case Groups	Cases	<18 Mos	<24 Mos	<36 Mos
All Cases	624	1.12 (0.91-1.38)	1.21 (0.93-1.57)	1.49 (1.04-2.14)
Boys	500	1.22 (0.97-1.54)	1.29 (0.96-1.73)	1.67 (1.10-2.53)
Girls	124	0.83 (0.52-1.30)	0.96 (0.55-1.68)	1.06 (0.51-2.20)
Aged 3-5 Yrs	214	1.08 (0.73-1.60)	1.66 (0.95-2.92)	2.34 (0.99-5.54)
Aged 6-10 Yrs	410	1.14 (0.90-1.46)	1.10 (0.82-1.49)	1.33 (0.89-1.98)

Demographic Case Subgroup Analyses For GA Birth Certificate Sample

Case Subgroup	Cases	<18 Mos	<24 Mos	<36 Mos
All Cases	311	0.93 (0.66-1.30)	0.99 (0.63-1.55)	1.23 (0.64-2.36)
Boys	243	0.94 (0.65-1.38)	1.01 (0.61-1.67)	1.64 (0.77-3.49)
Girls	68	0.79 (0.33-1.86)	0.84 (0.26-2.77)	0.24 (0.04-1.47)
Aged 3-5 Yrs	112	0.77 (0.39-1.50)	1.67 (0.60-4.67)	2.63 (0.51-13.5)
Aged 6-10 Yrs	199	0.98 (0.65-1.47)	0.87 (0.51-1.46)	1.09 (0.52-2.30)

Clinical Case Subgroup Analyses For Total Sample

Case Subgroup	Cases	<18 Mos	<24 Mos	<36 Mos
No pre-exist	390	1.07 (0.83-1.39)	1.44 (0.82-1.59)	1.51 (0.96-2.37)
Regression	80	1.37 (0.78-2.41)	1.30 (0.64-2.66)	1.45 (0.54-3.93)
With MR	376	1.06 (0.82-1.38)	1.09 (0.79-1.51)	1.21 (0.79-1.84)
Without MR	248	1.23 (0.87-1.73)	1.46 (0.93-2.30)	**2.45 (1.20-5.00)**

Clinical Case Subgroup Analyses For Birth Certificate Sample

Case Subgroup	Cases	<18 Mos	<24 Mos	<36 Mos
No pre-exist	187	1.05 (0.68-1.61)	1.02 (0.56-1.86)	1.82 (0.77-4.31)
Regression	31	0.83 (0.23-3.09)	0.41 (0.07-2.29)	0.69 (0.14-3.30)
With MR	179	1.13 (0.72-1.79)	0.96 (0.54-1.71)	0.82 (0.38-1.79)
Without MR	132	0.68 (0.40-1.16)	1.02 (0.47-2.22)	3.55 (0.74-17.1)

Other Demographic Subgroup Analyses For Birth Certificate Sample

Subgroup	Category	Cases	<18 Mo	<24 Mo	<36 Mo
Race	White/Oth	218	0.87	0.77	0.89
	Black	137	0.83	0.98	1.68
Maternal Age	<35 Yrs	295	0.90	0.91	1.23
	35+ Yrs	60	0.53	0.59	2.64
Maternal Ed	<16 Yrs	235	0.94	0.94	1.18
	16+ Yrs	120	0.60	0.61	2.76
Birth Weight	<2500 g	49	0.50	0.48	1.41
	≥2500 g	306	0.91	0.93	1.26

* No statistically significant associations for any subgroups in this table

Summary of Study Findings

- The variation in age of 1st MMR vaccination between children with autism and matched controls was similar
- No significant associations were found between vaccination at <18 or <24 months and risk for autism or for any autism subgroups including regression.

Summary of Study Findings

- Cases were more likely than controls to be vaccinated before 36 months of age.
- Profile for Elevated or Significant ORs:
  - Children aged 3-5 years
  - Boys
  - Children without MR
  - Children of Older Mothers
  - Children of Better Educated Mothers

Discussion

- Why 36 months and not 18 or 24 months?
  - In 1991, the Individuals with Disabilities Education Act (IDEA) mandated the provision of special education programs for children with autism beginning at 36 months
  - For school-based IDEA programs, GA required MMR vaccination
  - 98% of the autistic children aged 3-5 years were enrolled in preschool special education programs
  - Case children were identified primarily through these programs

Study Strengths

- Large population-based sample of children
- Clinical information reviewed by autism experts
- Most children received first MMR vaccination prior to publicity regarding possible association between MMR and autism
- Access to confounding variables from birth certificates
- Evaluation of ASD subgroups

Study Limitations

- Incomplete information available for determining age of onset for ASD
- Very small unexposed group
  - Most children received MMR vaccine by 36 months
  - Denmark Study had 20% of children unexposed
- MMR immunization records
  - Obtained from school records and could not be confirmed
  - Not available on all cases
- Confounders were only available for the GA State birth certificate sample
- Study was not initially designed to assess ASD subgroups

Study Conclusions

- Similar patterns of age at 1st MMR vaccination among cases and controls
- Similar proportions of cases and controls vaccinated according to ACIP schedule (i.e., <18 months)
- Similar proportions of cases and controls vaccinated by typical age of onset for autism (i.e. <24 months)
- Children with autism were more likely to be vaccinated before 36 months of aged compared to matched controls

The End