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

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CDC Collaborators

- National Immunization Program
  - William Thompson, PhD

- National Center on Birth Defects and Developmental Disabilities
  - Tanya Karapurkar, MPH
  - Marshalyn Yeargin-Allsopp, MD
  - Coleen Boyle, PhD
Background

- Two observations which may suggest a potential association between MMR vaccination and autism

1. Timing of initial recognition of autism symptoms occurs about the same time as recommended age for first MMR vaccination

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 suggesting no association
  - Biologic models which were fragmentary
  - No well defined animal models
  - Wakefield 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 1st MMR vaccine
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 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
    - Lack of appropriate eye contact
    - Unresponsive to parents’ voices
    - Unwilling to cuddle
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

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Retardation (MADDSP case def)</td>
<td>378</td>
<td>61%</td>
</tr>
<tr>
<td>Pre-existing conditions</td>
<td>235</td>
<td>38%</td>
</tr>
<tr>
<td>Regression and/or Plateau</td>
<td>80</td>
<td>13%</td>
</tr>
</tbody>
</table>

- ASD subgroups were not mutually exclusive
- Mental Retardation defined as 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

* Case children in special education schools were matched to controls from public school associated with case child’s home address
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)
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

Percentage of Total Sample

Cases

Controls

3-5 Yrs

6-10 Yrs
Descriptive Data

Sex Distribution of Cases and Controls

Percentage of Total Sample

Cases

Controls

Male

Female
Descriptive Data
Maternal Age from Birth Certificate

Percentage of total sample

Cases

Controls

< 20 Yrs
20 - 34 Yrs
35+ Yrs

< 20 Yrs
20 - 34 Yrs
35+ Yrs

0%
20%
40%
60%
80%
100%
Descriptive Data
Birth Weight from Birth Certificate

Percentage of total sample

Cases

Controls

0 - 1499 g
1500-2499 g
2500+ g
Descriptive Data
Multiplicity from Birth Certificate
Results
Age at 1st MMR Vaccination For Total Sample

<table>
<thead>
<tr>
<th>Age Group</th>
<th>%Cases</th>
<th>%Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 11 mo</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>12 - 17 mo</td>
<td>440</td>
<td>1232</td>
</tr>
<tr>
<td>18 - 23 mo</td>
<td>90</td>
<td>260</td>
</tr>
<tr>
<td>24 - 29 mo</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>30 - 35 mo</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>36+ mo</td>
<td>41</td>
<td>172</td>
</tr>
</tbody>
</table>

%Cases and %Controls
Demographic Case Subgroup Analyses
For Total Sample

<table>
<thead>
<tr>
<th>Case Groups</th>
<th>Cases</th>
<th>&lt; 18 Mos</th>
<th>&lt; 24 Mos</th>
<th>&lt; 36 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td>624</td>
<td>1.12</td>
<td>1.21</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.91-1.38)</td>
<td>(0.93-1.57)</td>
<td>(1.04-2.14)</td>
</tr>
<tr>
<td>Boys</td>
<td>500</td>
<td>1.22</td>
<td>1.29</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.97-1.54)</td>
<td>(0.96-1.73)</td>
<td>(1.10-2.53)</td>
</tr>
<tr>
<td>Girls</td>
<td>124</td>
<td>0.83</td>
<td>0.96</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.52-1.30)</td>
<td>(0.55-1.68)</td>
<td>(0.51-2.20)</td>
</tr>
<tr>
<td>Aged 3-5 Yrs</td>
<td>214</td>
<td>1.08</td>
<td>1.66</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73-1.60)</td>
<td>(0.95-2.92)</td>
<td>(0.99-5.54)</td>
</tr>
<tr>
<td>Aged 6-10 Yrs</td>
<td>410</td>
<td>1.14</td>
<td>1.10</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.90-1.46)</td>
<td>(0.82-1.49)</td>
<td>(0.89-1.98)</td>
</tr>
<tr>
<td>Case Subgroup</td>
<td>Cases</td>
<td>&lt; 18 Mos</td>
<td>&lt; 24 Mos</td>
<td>&lt; 36 Mos</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>All Cases</strong></td>
<td>311</td>
<td>0.93</td>
<td>0.99</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.66-1.30)</td>
<td>(0.63-1.55)</td>
<td>(0.64-2.36)</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>243</td>
<td>0.94</td>
<td>1.01</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.65-1.38)</td>
<td>(0.61-1.67)</td>
<td>(0.77-3.49)</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>68</td>
<td>0.79</td>
<td>0.84</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.33-1.86)</td>
<td>(0.26-2.77)</td>
<td>(0.04-1.47)</td>
</tr>
<tr>
<td>Aged 3-5 Yrs</td>
<td>112</td>
<td>0.77</td>
<td>1.67</td>
<td>2.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.39-1.50)</td>
<td>(0.60-4.67)</td>
<td>(0.51-13.5)</td>
</tr>
<tr>
<td>Aged 6-10 Yrs</td>
<td>199</td>
<td>0.98</td>
<td>0.87</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.65-1.47)</td>
<td>(0.51-1.46)</td>
<td>(0.52-2.30)</td>
</tr>
</tbody>
</table>
# Clinical Case Subgroup Analyses

## For Total Sample

<table>
<thead>
<tr>
<th>Case Subgroup</th>
<th>Cases</th>
<th>&lt; 18 Mos</th>
<th>&lt; 24 Mos</th>
<th>&lt; 36 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pre-exist</td>
<td>390</td>
<td>1.07 (0.83-1.39)</td>
<td>1.44 (0.82-1.59)</td>
<td>1.51 (0.96-2.37)</td>
</tr>
<tr>
<td>Regression</td>
<td>80</td>
<td>1.37 (0.78-2.41)</td>
<td>1.30 (0.64-2.66)</td>
<td>1.45 (0.54-3.93)</td>
</tr>
<tr>
<td>With MR</td>
<td>376</td>
<td>1.06 (0.82-1.38)</td>
<td>1.09 (0.79-1.51)</td>
<td>1.21 (0.79-1.84)</td>
</tr>
<tr>
<td>Without MR</td>
<td>248</td>
<td>1.23 (0.87-1.73)</td>
<td>1.46 (0.93-2.30)</td>
<td>2.45 (1.20-5.00)</td>
</tr>
</tbody>
</table>
## Clinical Case Subgroup Analyses
### For Birth Certificate Sample

<table>
<thead>
<tr>
<th>Case Subgroup</th>
<th>Cases</th>
<th>&lt; 18 Mos</th>
<th>&lt; 24 Mos</th>
<th>&lt; 36 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pre-exist</td>
<td>187</td>
<td>1.05</td>
<td>1.02</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.68-1.61)</td>
<td>(0.56-1.86)</td>
<td>(0.77-4.31)</td>
</tr>
<tr>
<td>Regression</td>
<td>31</td>
<td>0.83</td>
<td>0.41</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.23-3.09)</td>
<td>(0.07-2.29)</td>
<td>(0.14-3.30)</td>
</tr>
<tr>
<td>With MR</td>
<td>179</td>
<td>1.13</td>
<td>0.96</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.72-1.79)</td>
<td>(0.54-1.71)</td>
<td>(0.38-1.79)</td>
</tr>
<tr>
<td>Without MR</td>
<td>132</td>
<td>0.68</td>
<td>1.02</td>
<td>3.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.40-1.16)</td>
<td>(0.47-2.22)</td>
<td>(0.74-17.1)</td>
</tr>
</tbody>
</table>
Other Demographic Subgroup Analyses
For Birth Certificate Sample

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

* No statistically significant associations for any subgroups in this table
Summary of 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 Findings

- Cases were more likely than controls to be vaccinated before 36 months of age (93.4% vs. 90.6%).

- Profile for Elevated and/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.

- GA required MMR vaccination for school-based IDEA programs.

- In this sample, 98% of the ASD children aged 3-5 years were enrolled in preschool special education 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 available for only birth certificate sample
- Study was not designed to assess ASD subgroups
Summary

- 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