Exposure to Antibody-stimulating Proteins and Polysaccharides in Vaccines and Risk of Autism

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Continuing Concern about Vaccines and Autism

- 2004 IOM review
  - Evidence favors **rejection** of a causal association between MMR vaccine or thimerosal-containing vaccines and autism
- Parental concern persists
  - 25% - 30% of parents in recent surveys expressed concern that vaccines may cause learning disabilities such as autism
- “Too many too soon”
  - Many parents concerned that children get too many vaccines during the first two years of life and too many vaccines in one doctor’s visit
  - Current hypothesis is that autism is caused by “too many vaccines given too soon”

Refs: Freed 2010; Kennedy 2010

Primary Research Question

- Is the level of immunological stimulation from vaccines in the first two years of life associated with autism spectrum disorders (ASD) or sub-types of ASD?

Performed secondary analysis of VSD study of thimerosal and autism (Price 2010)

- Case-control study
  - 256 ASD cases
  - 752 controls
- Exposure assessment
  - Computerized MCO data
  - Medical chart abstraction
- Telephone interviews of cases and controls
- In-person evaluation of cases
  - ADOS and ADI-R for ASD diagnosis and sub-type classification
    - Autistic disorder (AD)
    - ASD with regression

Methods
Exposures and Exposure Periods

- "Immunogens" = antibody-stimulating proteins and polysaccharides in individual vaccines (adapted from Offit)
- Exposure periods
  - Birth to 7 months of age
  - Birth to 12 months of age
  - Birth to 24 months of age
- Exposure amounts during time period
  - Cumulative
  - Maximum on any single day

Types of Vaccines Received and Number of Immunogens in Each Type of Vaccine

Vaccine Type	Immunogens
DT TD	2
DTP	3,002
DTP-HIB	3,004
DTaP	4-6
DTaPHepB	6
Influenza	10
HIB	2
HepA	4
HepB	1
HepB-HIB	3
MMR	24
Measles	10
Meningococcus	2
Mumps	9
Pneumococcus	8
Polio	15
Rabies	5
Rotavirus	14
Rubella	5
Typhoid	3,000
Varicella	69
Yellow fever	11

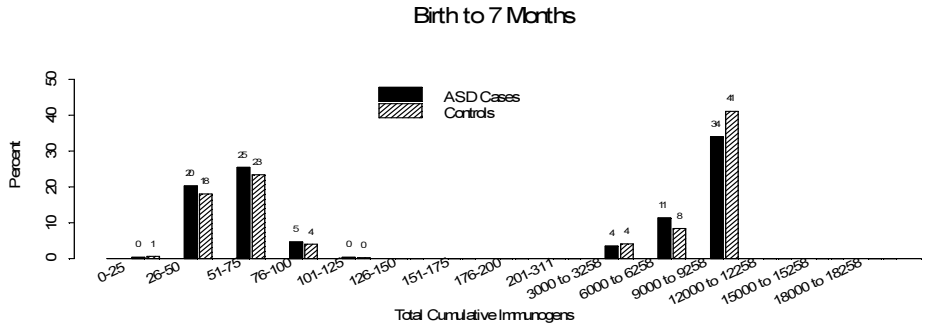
Statistical Analyses

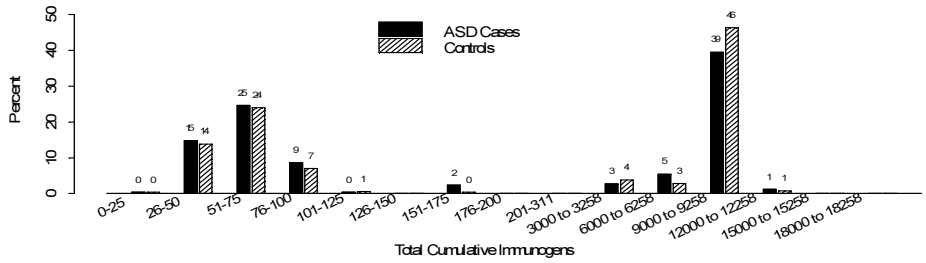
- Conditional logistic regression
- Separate models for cumulative and single day exposures in 3 age periods
- Adjusted for several factors
  - Child and family characteristics
  - Pregnancy and birth history
  - Maternal exposures during pregnancy
  - Early childhood health and exposures
  - Maternal health care seeking behavior

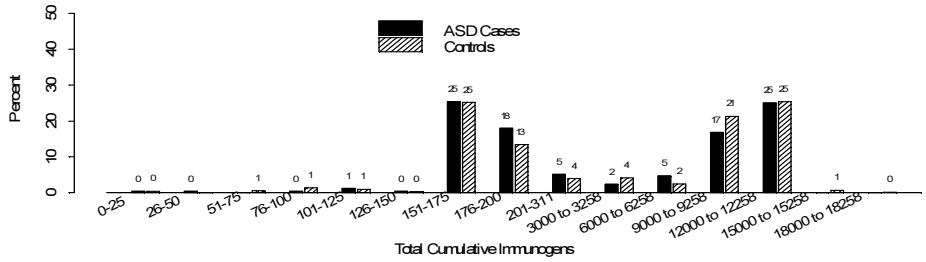
Results: Characteristics

Characteristic	ASD Casese (N=256), %	Controls (N=752), %
Sex		
Female	13	15
Male	87	85
Birth year		
1994-95	29	31
1996-97	37	37
1998-99	33	31
Child's age, median [range]	9 [6-13]	9 [6-13]

Distribution of Total Cumulative Immunogen Exposure among ASD Cases and Controls, by Age Range







Association between Cumulative Immunogen Exposure and Autism Outcomes

Exposure Measure/Period		Adjusted OR (95% CI) per 25 unit Increase in immunogens	
ASD Cases (n=256) vs Controls (n=752)			
	Birth to 7 months	0.9992	(0.9974,1.0010)
	Birth to 1 year	0.9995	(0.9976,1.0013)
	Birth to 2 years	0.9996	(0.9981,1.0012)
AD Cases (n=187) vs Controls (n=724)			
	Birth to 7 months	1.0007	(0.9973,1.0040)
	Birth to 1 year	1.0005	(0.9971,1.0038)
	Birth to 2 years	0.9999	(0.9971,1.0028)
ASD w/Regression Cases (n=49) vs Controls (n=652)			
	Birth to 7 months	0.9985	(0.9928,1.0043)
	Birth to 1 year	0.9983	(0.9926,1.0040)
	Birth to 2 years	0.9979	(0.9921,1.0038)

Association between Maximum Single Day Immunogen Exposure and Autism Outcomes

Exposure Measure/Period		Adjusted OR (95% CI) per 25 unit Increase in immunogens	
ASD Cases (n=256) vs Controls (n=752)			
	Birth to 7 months	0.9995	(0.9975,1.0015)
	Birth to 1 year	0.9994	(0.9974,1.0015)
	Birth to 2 years	0.9996	(0.9979,1.0014)
AD Cases (n=187) vs Controls (n=724)			
	Birth to 7 months	0.9986	(0.9936,1.0036)
	Birth to 1 year	0.9984	(0.9934,1.0035)
	Birth to 2 years	0.9979	(0.9928,1.0030)
ASD w/Regression Cases (n=49) vs Controls (n=652)			
	Birth to 7 months	0.9998	(0.9907,1.0090)
	Birth to 1 year	0.9996	(0.9905,1.0088)
	Birth to 2 years	0.9992	(0.9899,1.0085)

Summary

- 2004 IOM review concluded against a causal association between MMR or thimerosal-containing vaccines and autism
- Parents continue to be concerned that vaccines may cause autism, particularly from too many vaccines received too soon in early life
- Current study adds :
  - No increased risk of ASD associated with amount of immunological stimulation from vaccines in early life
  - No increased risk for ASD subtypes, including regression

Study Limitations:

- Reporting Bias?
  - Can be a concern in case-control studies
  - Post-natal exposure assessed only from computerized and paper medical records
- Assumes all proteins and polysaccharides are equally immunogenic
- Relevance to current immunization schedule?

Conclusion

Level of exposure to antibody-stimulating proteins and polysaccharides in vaccines in the first two years of life is not related to risk of autism spectrum disorders

Thank you

Extra Slides

Methods

- Parent Interview
  - Administered to both cases and controls
  - Data collection for confounders
    - Family demographics
    - Maternal/child medical history
    - Fish consumption - prenatal and postnatal
    - Other child exposures
  - Social Communication Questionnaire (SCQ)
    - Administered ONLY to controls as a screening tool
    - Assesses problems in social behavior, communication behaviors, or exaggerated interests or repetitive stereotyped play
    - SCQ Positive Control Children – excluded from the study

Methods
Clinical Case Assessment

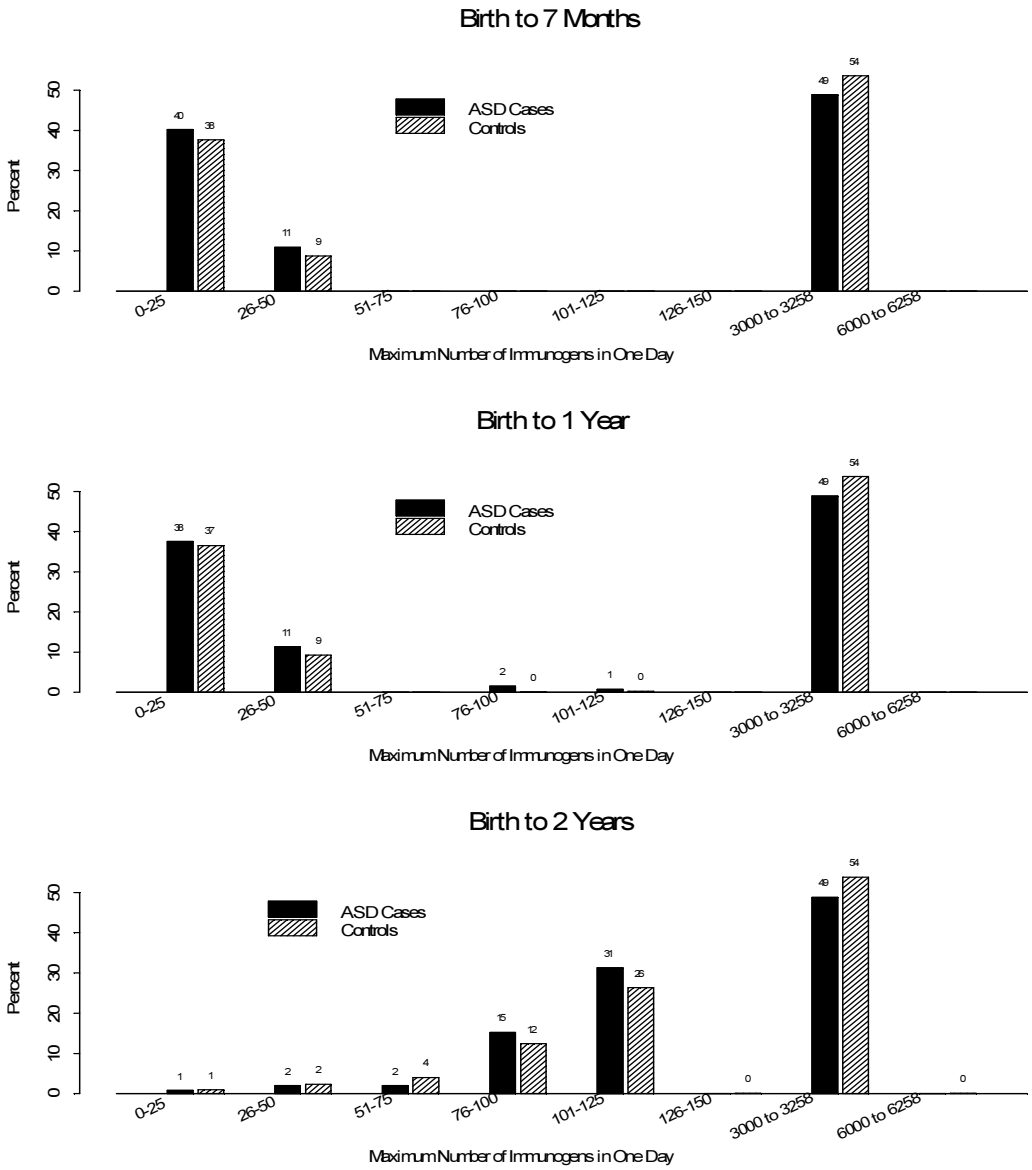
- Clinical interviews with mother
  - Autism Diagnostic Interview-Revised (ADI-R)
    - 3 hour semi-structured clinical interview
    - 111 items that focus on three domains
      - Quality of social interactions
      - Communication and language
      - Repetitive, restricted, and stereotyped behavior
  - Regression Interview
    - Measures regression in language, social skills, and play activities (relied on language to define regression)

Methods
Clinical Case Assessment Cont.

- Clinical assessment of case children
  - Autism Diagnostic Observation Schedule (ADOS)
    - 35-40 minute semi-structured observation of child
    - Administered by trained clinicians
  - Cognitive Measure
    - Raven's Colored Progressive Matrices
      - Measures novel problem solving
    - Mullen Scales of Early Learning
      - Visual Reception Scale
      - Valid for children aged birth to 6 years of age

Methods
Confirmed DX of Autistic Disorder

- Age of onset prior to 36 months
- Above threshold on three ADI-R (parent) domains
  - Reciprocal social interaction
  - Communication
  - Repetitive or restricted behaviors
- Above threshold on two ADOS (child) subscales and total score
  - Social Interaction
  - Communication
  - Communication-Social Interaction Total


Birth to 7 Months
Percent
0
10
20
30
40
50
ASD Cases
Controls
40
38
11
9
49
54
0-25
26-50
51-75
76-100
101-125
126-150
3000 to 3258
6000 to 6258
Maximum Number of Immunogens in One Day
Birth to 1 Year
Percent
ASD Cases
Controls
38
37
11
9
2
0
1
0
49
54
0-25
26-50
51-75
76-100
101-125
126-150
3000 to 3258
6000 to 6258
Maximum Number of Immunogens in One Day
Birth to 2 Years
Percent
ASD Cases
Controls
1
1
2
2
2
4
15
12
31
26
0
49
54
0
0-25
26-50
51-75
76-100
101-125
126-150
3000 to 3258
6000 to 6258
Maximum Number of Immunogens in One Day

Data Integrity

- External panel of consultants
- Detailed technical report
- Public use dataset