MMR and Autism

A review for the Global Advisory Committee on Vaccine Safety

Robert Davis, MD, MPH

University of Washington Departments of Pediatrics and Epidemiology
Group Health Cooperative Center for Health Studies
CDC Vaccine Safety Datalink Project

Introduction

Published research on MMR vaccine safety

- MMR2: A comparison of adverse events after MMR given at 4-6 years and 10-12 years of age. *Pediatrics*.1997
- MMR and Other Measles-Containing Vaccines Do Not Increase Risk for Inflammatory Bowel Disease. *Arch Pediatr Adolesc Med*, 2001
- Measles Vaccination and Inflammatory Bowel Disease: Controversy Laid to Rest? *Drug Safety*, 2001

Other vaccine safety studies

- The Impact of the Change in Polio Vaccination Schedule on Immunization Coverage Rates. *Pediatrics*. 2001
- Seizures following Pertussis or Measles Vaccination: Risks and Long Term Outcomes. *N Engl J Med*, 2001

Introduction

Ongoing studies of

- Ataxia following vaccination
- DTP given to children with seizure disorders
- DTPa and seizures

Planning studies of

- Autism and prenatal, neonatal, and infant thimerosal/mercury/MMR exposure
- Rapid cycle analysis of vaccine safety

Overview of talk

Brief review of autism and autism-spectrum disorder

General approach to summary

Brief Summary of past reviews

1. Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism. Institute of Medicine
2. Measles-Mumps-Rubella Vaccine and Autistic Spectrum Disorder: Report from Childhood Immunizations Conference, 2000.
3. Measles-mumps-rubella vaccine and autistic spectrum disorder: A hypothesis only. Canadian Pediatric Society. 2001

Review of epidemiologic evidence

- In-depth review of individual studies – strengths and weaknesses
- Summary of studies by analytic type

Review of laboratory-based evidence

Summary and Conclusions

Overview of Autism and Autism-Spectrum Disorder (ASD)

Autism

Complex and severe neurodevelopmental disorder
Strong male preponderance

Primarily characterized by impairments of
- Social interaction
- Verbal and nonverbal communication
- Restricted/stereotypical patterns of behaviors

Onset of symptoms typically in second year of life (although recent research suggests might be earlier to trained observer)

Overview of Autism and Autism-Spectrum Disorder (ASD)

Autism

Anatomic findings suggest prenatal insult:

Decreased cell size, increased cell density; cerebellar and Purkinje cell abnormalities; preservation of olivary neurons

Genetic studies suggest strong gene mediated influences

- High concordance rate in monozygotic >> dizygotic twins
- High recurrence rate in sibs
- Associated with other genetic disorders including fragile X, tuberous sclerosis, Turner's syndrome

Overview of Autism and Autism-Spectrum Disorder (ASD)

Autism-Spectrum Disorder (ASD)

- Continuum of disorders with varied severity of deficits and level of cognitive development
- Includes Aspergers, Pervasive developmental disorder (PDD)

Overview of Autism and Autism-Spectrum Disorder (ASD)

Rates of autistic disorder

- 23 epidemiologic studies between 1966 – 1998
- Prevalence ranged 0.7 – 21.1 per 10,000
- Median 5.2 per 10,000

Rates of autistic spectrum disorder

- Prevalence 1-6 per 1,000

Studies vary considerably with intensity of case ascertainment methods

General approach to summary

No presumption that MMR does, or doesn't, cause Autism or ASD

Evidence is evaluated for whether it favors acceptance or rejection of causal relationship

Evidence showing no association required to reject causal relationship

Absence of evidence, or inadequate evidence, doesn't favor rejecting causality

Biologic plausibility in absence of adequate epidemiologic evidence is not sufficient to influence causality argument

Review of past summaries

Institute of Medicine summary (IOM)

- Evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD
- Does not exclude possibility that MMR vaccine could contribute to ASD in a small number of children

Childhood Immunizations Conference (H) summary

- Available evidence does not support hypothesis that MMR vaccine causes autism or associated disorders or IBD

Canadian Pediatric Society summary (CPS)

- Evidence available internationally to date does not support an association between MMR vaccination and the development of autism

Review of past summaries

These reviews assessed 6 or fewer published epidemiologic studies

Taylor (1999)	H	CPS	IOM
Kaye	H	CPS	IOM
Dales	H	CPS	IOM
Peltola		CPS	IOM
Gillberg		CPS	IOM
Patja			IOM

Since then, studies by:

Madsen et al: A population based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002

Farrington et al:MMR and autism: further evidence against a causal association. Vaccine 2001

DeWilde et al: Do children who become autistic consult more often after MMR vaccination? Brit J of General Practice 2001

Fombonne: No evidence for a new variant of measles-mumps-rubella induced autism. Pediatrics 2001

Taylor et al: Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study BMJ 2002

Summary of epidemiologic studies

Yr	Author	Years	Type	Cases
1998	Peltola	1982-1996	Follow up w/o ref group	31
1998	Gillberg	1975-1988	Ecologic	55
•	Taylor	1979-1992	Case-crossover	498
•	Farrington	1979-1998	Case crossover	357
2000	Patja	1982-1006	Follow-up w/o ref group	0
2001	Kaye	1988-1999	Ecologic	305
2001	Fombonne	1954-1996	Ecologic (case v case analysis)	262
2001	DeWilde	1989 – present	Case control	71
2001	Dales	1980-1994	Ecologic	N.S.
2002	Taylor	1979-1998	Case-crossover Ecologic	278
2002	Madsen	1991-1998	Cohort	738

Title	No evidence for MMR vaccine-associated inflammatory bowel disease or autism in a 14 year propsective study
Author	Peltola
Journal	Lancet
Year Published	1998
Years Covered	1982-1996
Type of Study	Cohort follow-up without comparison group, of vaccinees who developed GI symptoms following vaccination
Specific Hypothesis	Were there children who developed GI symptoms shortly after vaccination who then went on to develop IBD and/or autism
Number of cases	31 children developed GI symptoms after vaccination

Title	No evidence for MMR vaccine associated inflammatory bowel disease or autism in a 14 year prospective study
Findings	31 children were followed for at least 16 months, and some up to 181 months (15 years). Most had diarrhea with vomiting after vaccination No child developed autistic spectrum disorder
Limitations	Low power to detect true effect severely limits any conclusions (0 events/31 ~ upper 95th CI approx 9%)
Conclusion	Relatively non-contributory

Title	MMR and autism
Author	Gillberg
Journal	(Autism)
Year Published	1998
Years Covered	1975-1984 birth cohort
Type of Study	Ecologic
Specific Hypothesis	Did introduction of MMR vaccination in 1982 increase rate of autism in Sweden
Number of cases	74

Title	MMR and autism
Findings	MMR vaccine introduced 1982 Rate of autism calculated for children born 1975-1980 (5.5 y) and compared to rate among those born 1980-1984 (4.5 y) 47 children born during earlier period 27 children born during later period
Limitations	Different number of years in the denominator Different length of follow in the earlier vs later times. Diagnoses made after 4 years of age (after 1988) in the latter cohort would have been missed Assumption that number of children born each year remained stable Limited power (55 cases of autism; 74 overall) Lack of face validity; almost all other studies have shown autism increasing over time. Before/after studies as this one should show some relation, however spurious
Conclusion	Limited evidence against relationship between vaccine and autism

Title	Autism and MMR vaccine: no epidemiological evidence for a causal association
Author	Taylor
Journal	Lancet
Year Published	1999
Years Covered	1979-1992
Type of Study	Case-crossover Ecologic
Specific Hypothesis	Did autism increase after MMR introduced in 1988 Did age at diagnosis change after MMR introduced Was there clustering of cases after MMR
Number of cases	498 cases of autism 293 confirmed by ICD 10 criteria

Title	Autism and MMR vaccine: no epidemiological evidence for a causal association
Findings	Cases ascertained by computerized registries at child developmental centers and special schools
	Age of autism diagnosis compared for children receiving MMR before 18 months, after 18 months, and never
	Case crossover analysis for periods within 1-2 years for autism, within 6-12 months for parental concerns, and within 2,4, and 6 months for regression
	No evidence of step up in birth cohorts exposed to vaccine, nor change in slope of curve (from exponential slope)
	During period of most rapid increase in autism, MMR coverage by second year of life was stable
	No difference in age of autism onset among children receiving vaccination before or after 18 months of age, or never receiving vaccine
	No clustering of autism, parental concern, or regression in time windows after vaccination, except for parental concern 6 months after vaccination
	(Authors interpretation for number preference (6 mo) following age of most frequent vaccination
Limitations	No standardized assessment of regression timing
	No standardized evaluation of cases
Conclusion	Evidence against a relationship between vaccination and triggering of symptoms. Evidence against increase in disease after MMR introduction

Title	Serious adverse events after MMR vaccination during a fourteen year prospective follow-up
Author	Patja
Journal	Pediatr Infect Dis J
Year Published	2000
Years Covered	1982-1996
Type of Study	Cohort follow-up without comparison group
Specific Hypothesis	To perform surveillance for serious adverse events after MMR over 14 years
Number of cases	1.8 million individuals immunized, with 3 million vaccine dose

Title	Serious adverse events after MMR vaccination during a fourteen year prospective follow-up
Findings	Country-wide passive surveillance system collected AE reports At start of project in 1982, seminars, media, medical publications used to highlight system No cases of autism were reported following vaccination
Limitations	At rate of 6/1000 for ASD or 6/10,000 for Autism, should have been hundreds/thousands of cases, regardless of causal association Since no cases were reported, implication is that reporting was limited to those diseases known to be associated with vaccination
Conclusion	Non-contributory

Title	MMR and autism: further evidence against a causal association
Author	Farrington
Year published	2000
Journal	Vaccine
Years covered	1979 - 1998
Type of study	Case-crossover

Specific hypothesis	Extended their previous study that looked at clustering of autism following vaccination.
	Looked 'all' time intervals, including risks
	within 5 years after vaccination for autism diagnosis
	within 3 years for parental concern
	within 2 years for regression

Number of cases	357 with autism

Title MMR and autism: further evidence against a causal association

In depth review of findings

Risk for autism following MMR was compared to the risk for autism before MMR. (Distribution of age at autism diagnosis of 64 unvaccinated children with autism were used to adjust for age, with 16 categories used to control for time)

No increased risks for autism diagnosis, for parental concern, or for regression when all time following vaccine is compared with all time prior to vaccine.

No risk for autism within 5 years, for parental concern within 3 years, or for regression within 2 years.

Limitations

Brief discussion of methods.

No discussion of case ascertainment or validation.

Misclassification of case, or of regression, would bias towards null.

Time after vaccination is older than time prior to vaccination: unclear whether age adjustment can adequately adjust for this.

Conclusions

Evidence against an ever-never effect and evidence against a triggering phenomenon

Title	Time Trends in Autism and in MMR immunization coverage in California
Author	Dales
Journal	JAMA
Year Published	2001
Years Covered	1980-1994
Type of Study	Ecologic
Specific Hypothesis	Did autism case load in California increase as immunization coverage with MMR increased?
Number of cases	Not described

Title	Time Trends in Autism and in MMR immunization coverage in California
Findings	Cohort born between 1980 – 1994 Assumed autism ascertainment complete for children born in 1994 Autism caseload increased each year: one rate 1980 – 1984 another rate 1985 - 1988 another rate 1988 – 1994 The major rise in caseload was after 1988, while MMR coverage at 17 and 24 months was constant _First_ rise in autism caseload was in 1985, before any rise in MMR coverage
Limitations	State immunization records possibly incomplete (exposure validity questionable) Had coverage increased, but not recorded, might have missed positive association Autism validation non-existent Caseload used rather than _rates_ Complete case ascertainment not attempted No individual level data on exposure or outcome
Conclusion	Weak evidence against association. Fair evidence against MMR as a major influence of autism rates

Title	MMR vaccine and the incidence of autism recorded by general practitioners: a time trend analysis
Author	Kaye
Journal	BMJ
Year Published	2001
Years Covered	1988-1999
Type of Study	Ecologic
Specific Hypothesis	Did risk for autism increase with increasing MMR vaccine coverage?
Number of cases	305 children with first recorded autism diagnosis between 1988 and 1999. Subanalysis of 114 boys born 1988-1993 to provide rates for children 2-5 years old between 1990 and 1999

Title	MMR vaccine and the incidence of autism recorded by general practitioners: a time trend analysis
Findings	Used the UK GPRDatabase Vaccine coverage stated as complete 81% of cases were evaluated by specialists For each birth cohort, estimated the cumulative risk for autism between 2 to 5 years of age Risk increased from 8/10,000 born in 1988 to 29/10,000 born in 1993 MMR vaccination by 2 years of age constant at 97%
Limitations	Autism not validated by strict criteria (but doubtful that entire rise in case-load was due to increasing misclassification)
Conclusion	Evidence against an association

Title	Do children who become autistic consult more often after MMR vaccination
Author	DeWilde
Journal	British Journal of General Practice
Year published	2001
Years covered	1989 - present
Type of study	Case control

Specific hypothesis

Do children with autism see providers and/or get consultations more frequently after MMR vaccination than children without autism

Exposure	MMR vaccine
Outcome	Consultation rates (for symptoms)
Number (cases)	71

Title Do children who become autistic consult more often after MMR vaccination

In depth review of findings

If vaccination caused increase in symptoms – one would see a preferential increase in symptoms and consultations following vaccination for cases but not for children without autism.

Study performed in the Doctors Independent Network; 127 core practices with data on children enrolled from birth, in the UK. First started in 1989

Children with autism diagnoses prior to vaccination were excluded (one case)

Controls were matched by practice, age, gender, month of vaccination, and current enrollment

The rates of consultations fell after MMR vaccination among both cases and among controls. The rates of fall did not differ statistically (significantly or clinically) between the two. No case was diagnosed in the 6 months following MMR

Limitations

Autism criteria was not confirmed.

May have missed some, or many, cases; wouldn't necessarily bias results

Timing of autism diagnosis was not specified.

Conclusion:

Evidence against MMR triggering symptoms that are eventually diagnoses as autism

Title	No evidence for a new variant of MMR induced autism
Author	Fombonne
Journal	Pediatrics
Year Published	2001
Years Covered	3 birth cohort samples: 1992-1995 (post MMR) 1987-1996 (post MMR) 1954-1979 (pre MMR)
Type of Study	Ecologic
Specific Hypothesis	Has age at diagnosis changed in post MMR samples? Have rates of regression increased in post MMR samples? Is age of regression diagnosis or concern younger than those without regression? Is interval between immunization and concern shorter in children with regression?
Number of cases	262 in 3 samples

Title	No evidence for a new variant of MMR induced autism	
Findings	Avg age of diagnosis:	19 months in pre and post samples
	Avg age of concern:	19 months for regression and non-regressive autism
	Lag between MMR and concern was	248 d for regression
		272 for non-regressive
	Proportion of cases with regression	18% in pre-MMR sample
		16% in post MMR sample
Limitations	MMR might increase rate of autism without altering avg. age at diagnosis	
	Comparing lag between MMR and concern for regression versus concern for non-regressive cases is based on 67 children total: limited power to detect differences as statistically significant	
	Difficult to interpret results based on comparisons with pre-sample that goes back to 1954. Case ascertainment and diagnostic criteria likely to differ substantially in years prior to 1979 compared with years 1987-1996	
Conclusion	Limited evidence against relationship between vaccine and autism	

Title	MMR vaccine and bowel problems or developmental regression in children with autism: population study
Author	Taylor
Journal	BMJ
Year Published	2002
Years Covered	1979-1998
Type of Study	Case-crossover
Specific Hypothesis	Relationship of MMR with bowel problems for more than 3 months, and regression
Number of cases	278 children with autism, and 195 with 'atypical' autism 81 had bowel problems 118 (25%) had regression

Title	MMR vaccine and bowel problems or developmental regression in children with autism: population study
Findings	No trends by year of birth in % of children with autism who also had bowel problems, or of children with autism and regression. This spanned the period when MMR was introduced
	Of children with bowel problems and autism 19% of children vaccinated before parental concern 15% vaccinated after parental concern 16% never vaccinated (p=0.48)
	Of 28 children with 'autistic enterocolitis' (signs and symptoms), no association with MMR vaccination (p=0.57) nor with year of birth in the proportion of these symptoms
	Of 31 children with bowel problems and regression no association with MMR vaccination (p=0.20) nor with year of birth
Limitations	Low power to assess association between 'autistic enterocolitis' and MMR vaccination No OR given for MMR vaccination association; p values only (no CI)
Conclusion	No evidence to support new variant of regressive autism with bowel problems or clustering following vaccination Evidence for association between regression and bowel disease, just not with vaccination

Title	A population based study of MMR vaccine and autism
Author	Madsen
Journal	NEJM
Year Published	2002
Years Covered	1991-1998 birth cohort
Type of Study	Population based retrospective cohort
Specific Hypothesis	Was ever receiving MMR vaccination linked to cumulative risk for developing autism
Number of cases	738

Title	A population based study of MMR vaccine and autism
Findings	MMR vaccine introduced 1987 Cases obtained from Danish Psychiatric Central Register Reporting felt as complete due to comprehensive case surveillance in Denmakr Prevalence 2.22/1000 ASD; therefore likely complete Only specialists in child psychiatry diagnose autism/assign diagnostic codes Case coding based on ICD 10 Cart review of 40 children to validate coding: 37 met CDC Brick Township Criteria; other 3 met ASD criteria Adjusted for age, gender, time, SES, maternal education, gestational age, BW 440,000 children vaccinated 96K unvaccinated RR for vaccination vs unvaccination: 0.92 (0.68 – 1.24) for autism 0.83 (0.65 – 1.07) for ASD RR did not vary by time since vaccination (no clustering) Only cohort study with exposure and outcome data at the individual level
Limitations	No information on why children did not get vaccinated No information on regression Exclusion of fragile X, Angelmans (other causes of autism) relied on identifying those who were hospitalized: unlikely to be complete
Conclusion	Strong evidence against MMR increasing risk for autism among vaccinated vs unvaccinated children; Evidence against triggering

Summary of Ecologic Studies

Study	Year	Findings
Gilberg	1998	Evidence against association with autism
Taylor	1999	Evidence against association with autism
Kaye	2001	Evidence against association with autism
Dales	2001	Evidence against association with autism
Fombonne	2001	Evidence against association with autism
Taylor	2002	Evidence against association with regression

Summary of ‘triggering’ hypothesis

Study	Year	Findings
DeWilde	2001	Evidence against an association with triggering
Farrington	2000	Evidence against triggering over longer time periods
Taylor	1999	Evidence against triggering
Madsen	2002	Evidence against triggering

Summary of ‘triggering regression’ hypothesis

Study	Year	Findings
Taylor	1999	Evidence against triggering regression
Taylor	2002	Evidence against triggering regression
(Fombonne	2001	Evidence against, from case vs case analysis)

Summary of ‘ever/never’ hypothesis

Study	Year	Findings
Madsen	2002	Evidence against an association with autism
Farrington	2002	Evidence against an association with autism

Summary of lab-based investigations

Year/Author	Journal	Title
2000 Kawashima	Dig Dis Sci	Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism
2002 Martin	Mol Psych	Detection of measles virus in children with ileo-colonic lymphoid nodular hyperplasia, enterocolitis, and developmental disorder
2002 Singh	J biomed sci	Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism

Brief overview

2000 Kawashima Dig Dis Sci — Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism

Findings:

- 12.5% - 33.3% measles virus detection rates in PBMC preparations of Crohns dx, UC, and autistic enterocolitis
- 9 children with ‘autistic enterocolitis’ (8 with Crohn’s and 3 with ulcerative colitis)
- 3 of 9 children with autism were positive for specific regions of H and F gene regions
- Sequences from patients with autism were consistent with vaccine strains

Brief overview

2000 Kawashima Dig Dis Sci

Limitations:

In 5 prior studies,

Tissue samples:	Expected
0/56 Crohns	7
0/33 UC	11

Blood

0/16 Crohns	2
0/11 UC	4

Cross contamination of samples with measles virus controls or with pre-existing DNA templates?

Sample to sample variations between different PCR products of same sample

Brief overview

2002 Singh J Biomed Sci Abnormal Measles-Mumps-Rubella Antibodies and CNS Autoimmunity in Children with Autism

Findings:

125 children with autism
92 control children

Unusual MMR antibody and antibodies to myelin basic protein in 75/120 (60%) of autistic sera
0/ 92 control sera

Conclusions:

Postulated link between MMR antibody and antibody to myelin basic protein in children with autism. Autoimmunity from vaccination as a process in developing autism

Brief overview

2002 Singh

Limitations:
(Bellini)

Control children are not age and sex matched

Autism history not confirmed

Timing of past immunization not given (will affect antibody levels)

Use of an MMR antibody is not accepted widely

Immune response that occurs is to the separate components of MMR (no combination of viral RNA occurs among these viruses)

The authors use an in-house ELISA to detect “MMR antibodies”; not a valid/substantiated technique

Summary

Consistent evidence from ecologic, case-control, case-crossover, and cohort studies showing lack of an association between MMR vaccine and an increased risk for developing autism, either in the short time window following vaccination or at times distant from vaccination

Questionable evidence from two labs that measles virus is detectable in children with autism. Even if true, etiologic role far from established

Recommendations

Doubtful that further epidemiologic study can more convincingly answer this question than already answered

As with the inflammatory bowel disease question, independent confirmation of laboratory findings will be crucial to understanding the validity of the preliminary findings of Kawashima and Singh