Lack of Association Between Measles-Mumps-Rubella Vaccination and Autism in Children

A Case-Control Study

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Objective: The first objective of the study was to determine whether there is a relationship between the measles-mumps-rubella (MMR) vaccination and autism in children. The second objective was to examine whether the risk of autism differs between use of MMR and the single measles vaccine.
Design: Case-control study.
Study Population: The 96 cases with childhood or atypical autism, aged 2 to 15, were included into the study group. Controls consisted of 192 children individually matched to cases by year of birth, sex, and general practitioners.
Methods: Data on autism diagnosis and vaccination history were from physicians. Data on the other probable autism risk factors were collected from mothers. Logistic conditional regression was used to assess the risk of autism resulting from vaccination. Assessment was made for children vaccinated (1) Before diagnosis of autism, and (2) Before first symptoms of autism onset. Odds ratios were adjusted to mother's age, medication during pregnancy, gestation time, perinatal injury and Apgar score.
Results: For children vaccinated before diagnosis, autism risk was lower in children vaccinated with MMR than in the nonvaccinated (OR: 0.17, 95% CI: 0.06–0.52) as well as to vaccinated with single measles vaccine (OR: 0.44, 95% CI: 0.22–0.91). The risk for vaccinated versus nonvaccinated (independent of vaccine type) was 0.28 (95% CI: 0.10–0.76). The risk connected with being vaccinated before onset of first symptoms was significantly lower only for MMR versus single vaccine (OR: 0.47, 95% CI: 0.22–0.99).
Conclusions: The study provides evidence against the association of autism with either MMR or a single measles vaccine.

Key Words: MMR vaccine, autism, children

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A great deal of speculation exists concerning the possible associations of certain vaccines, particularly the measles-mumps-rubella (MMR) vaccine, with autism. Wakefield et al[1] were the first to propose that the MMR vaccine might be causally linked to autism. It was suggested that gastrointestinal and developmental symptoms constituted a syndrome that might be triggered by this vaccine. Their study was widely criticized but generated immense media attention, leading to a fall in MMR coverage in some European countries.[2–5] Since that report, a number of other studies have found no evidence to support a link between MMR vaccination and autism.[6–9]

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Although Poland continues to report high MMR vaccination coverage, questions concerning the safety of this vaccine, boosted by periodic antivaccination campaigns, persist. The MMR vaccine was introduced in Poland later than in most other European countries. For the past 10 years, the MMR vaccine has been gradually replacing the single-antigen measles variety. When it was first introduced, MMR was not covered by the national health service of Poland. Parents who wished to vaccinate their children with MMR, as opposed to the single mandatory measles vaccine, had to pay extra. For this reason, few children were immunized with MMR. The Polish mandatory vaccinations schedule did not include MMR for all children until 2004. Since then, already high levels of immunization against measles have slightly grown.[10] Poland's heterogeneous population (ie, vaccinated with MMR, vaccinated against measles only, nonvaccinated) serves as a unique sample group for studying the debated association of these vaccines with autism in children. Although a wide variety of published studies fail to find any such influence or relationship, the association between MMR and autism remains in the minds of some medical workers and parents. This way of thinking threatens to undermine the implementation of measles elimination programs.[11–13]

The first objective of this study was to determine whether a relationship exists between MMR vaccination and autism in children. The second objective was to examine whether the risk of autism differs between MMR and the single measles vaccine.

MATERIALS AND METHODS

Study Population

Subjects were identified using general practitioner records in the Lesser Poland (Małopolska) Voivodeship in Poland. The sample population of this study included children aged 2 to 15 years diagnosed with childhood or atypical autism, classified according to ICD 10-criteria as F84.0 or F84.1, respectively. Every diagnosis of autism was made by child psychiatrist. Dates of these diagnoses were recorded in general practitioners files. Cases with uncertain diagnosis of autism, secondary to disease state or trauma, were excluded. Two controls were selected for each affected child, individually matched by year of birth, gender, and physician's practice. The first 2 children visited the physician after the time of the autistic child visit who met entry criteria served as controls.

Questionnaire to the Parents of Affected Children and Controls

Parents were interviewed by trained nurses using a standardized questionnaire. Questions for all children included information about prenatal and postnatal development, mental and physical development, chronic diseases, malformations and injuries, history of bowel disturbances, birth order, family size, and parents' socioeconomic status.

Parents of children with autism were additionally asked about the date of onset of symptom, the period when parents first

suspected their child's symptoms might be related to autism, and their knowledge and beliefs regarding the cause of autism. This questionnaire did not contain any questions concerning the child's vaccination history so as to not bias the parent's answers (ie, insinuate a relationship with autism).

Autism Diagnosis and Vaccination History

The date of the child's autism diagnosis as well as his or her vaccination history was extracted directly from the physician's records.

Data Analysis

Cases of autism were considered as vaccinated if vaccination preceded the onset of symptoms. Controls were considered vaccinated if they received their vaccination before age of symptoms onset of their matched case subject. Conditional logistic regression analysis was used to examine the association between MMR vaccination and autism in the matched case-control analysis. The odds ratios were calculated for vaccinated versus nonvaccinated children, vaccinated with the single measles vaccine versus nonvaccinated, vaccinated with MMR versus nonvaccinated, and vaccinated with MMR versus the single measles vaccine. This procedure was repeated for vaccination preceding the time of autism diagnosis.

Other potential risk factors of autism (mother's age, mother's education, gestation time, medication during pregnancy, perinatal injury, and Apgar scale score) were examined and those that appeared to be associated with autism ($P < 0.2$) were carried forward into multivariate models. The statistical significance was defined as $P < 0.05$. Statistical analyses were performed using STATA 8.0.

RESULTS

The study population consisted of 96 cases and 192 controls, with a mean age 7.5 ± 2.6 years, 81.2% boys and 19.8% girls. Approximately 13% of case-group mothers were aged ≥35 years at time of delivery compared with 7.2% of control-group mothers. This represented a statistically significant difference (Table 1). Gestation time ≤38 weeks was also significantly more frequent in cases than controls. The mothers of autistic children significantly more often took medication during pregnancy (mostly antibiotics and antihypertensive drugs). Case-group subjects significantly more often suffered from some form of perinatal injury. Although the difference was not significant, 5-minute Apgar scores were often less than 9 in autistic children. These 5 factors were taken as potential confounders and included in multivariate analysis.

TABLE 1. Case- and Control-Group Characteristics

Characteristic	Cases (n = 96)		Controls (n = 192)		Statistical Significance
	N	%	N	%	
Mother aged ≥35 yr	12	12.9	14	7.3	0.013
Mother completed university education	29	30.5	68	35.6	0.43
Gestation time ≤38 wk	21	21.9	21	11.0	0.021
Medication during pregnancy	43	44.8	50	26.0	0.002
Perinatal injury	13	13.5	9	4.7	0.016
5-min Apgar scale score <9	17	17.7	20	10.4	0.094

Case-group parents recognized abnormal behavior by age 1 year in 40% of their children. This number rose to 69.8% by age 2 years. A diagnosis of autism was confirmed in 45.8% of children by age 2 years, in 22.9% by age 3 years, 21.9% by age 4 years, and 9.4% were diagnosed at age >4 years.

Most children (64.6% of cases and 76.6% of controls) were vaccinated at age 12 to 18 months. Across both groups, there were 9 children not vaccinated against measles (Table 2). The percentage of nonvaccinated children was significantly higher ($P = 0.001$) in cases than in controls. The MMR vaccine was used in 44.3% of vaccinated cases and 55.0% of vaccinated controls. This difference was not statistically significant.

Odds ratios of having autism, based on vaccination status and type of vaccine used, are presented in Table 3. Using logistic univariate regression modeling, no positive association was found

TABLE 2. Vaccination Practices, Before the Diagnosis of Autism, and Before Onset of Symptoms

Status	Children With Autism		Control Group	
	N	%	N	%
Vaccinated before symptom onset*				
No	26	27.1	44	22.9
Monovalent vaccine	39	40.6	61	31.8
MMR	31	32.3	87	45.3
Vaccinated before diagnosis†				
No	17	17.7	9	4.7
Monovalent vaccine	45	46.9	81	42.2
MMR	34	35.4	102	53.1
Ever vaccinated				
No	8	8.3	1	0.5
Monovalent vaccine	49	51.0	86	44.8
MMR	39	40.6	105	54.7

For the control group:
*Vaccinated before age of symptom onset of their matched case-group subject.
†Vaccinated before age of autism diagnosis of their matched case-group subject.

TABLE 3. Association Between Single Measles and MMR Vaccination Before the Diagnosis of Autism and Before Onset of Symptoms, Based on Univariate Modeling

Status	OR	95% CI	Statistical Significance
Vaccinated (independent of vaccine type) vs. nonvaccinated			
Vaccinated before symptom onset	0.56	0.24–1.30	ns
Vaccinated before diagnosis	0.23	0.09–0.57	$P = 0.001$
Single and MMR vaccination vs. nonvaccinated			
Vaccinated before symptom onset*			
Single vaccine	0.73	0.30–1.73	ns
MMR	0.39	0.16–0.98	$P = 0.045$
Vaccinated before diagnosis†			
Single vaccine	0.29	0.12–0.73	$P = 0.008$
MMR	0.16	0.07–0.41	$P < 0.001$
MMR vs. single vaccine			
Vaccinated before symptom onset	0.53	0.28–1.02	$P = 0.059$
Vaccinated before diagnosis	0.53	0.29–0.97	$P = 0.040$

For the control group:
*Vaccinated before age of symptom onset of their matched case-group subject.
†Vaccinated before age of autism diagnosis of their matched case-group subject.
ns indicates not significant.

TABLE 4. Association Between Single Measles and MMR Vaccination Before the Diagnosis of Autism and Before Onset of Symptoms, Based on Multivariate Modeling

Status	OR*	95% CI	Statistical Significance
Vaccinated (independent of vaccine type) vs. nonvaccinated			
Vaccinated before symptom onset	0.65	0.26–1.63	ns
Vaccinated before diagnosis	0.28	0.10–0.76	$P = 0.012$
Single and MMR vaccines vs. nonvaccinated			
Vaccinated before symptom onset†			
Single vaccine	0.86	0.33–2.23	ns
MMR	0.42	0.15–1.16	ns
Vaccinated before diagnosis‡			
Single vaccine	0.36	0.13–1.00	$P = 0.050$
MMR	0.17	0.06–0.52	$P = 0.002$
MMR vs. single vaccine			
Vaccinated before symptom onset	0.47	0.22–0.99	$P = 0.046$
Vaccinated before diagnosis	0.44	0.22–0.91	$P = 0.026$

*Adjusted for mother's age (15–35, 36–44 years), medication during pregnancy, gestation time (36–37, 38–43 weeks), perinatal injury, 5-minute Apgar scale score (3–8, 9–10).

For the control group:

†Vaccinated before age of symptom onset of their matched case-group subject.

‡Vaccinated before age of autism diagnosis of their matched case-group subject.

ns indicates not significant.

between measles vaccination and autism: all relative risks were below 1 and showed that vaccinated children, especially those with MMR, had a smaller risk of autism. Analyzing vaccination status before diagnosis demonstrated a very low odds ratio for vaccinated versus nonvaccinated. This tendency was slightly stronger for those vaccinated with MMR versus nonvaccinated, then the single measles variety versus nonvaccinated. Also, children vaccinated with MMR had a risk equal to half of those vaccinated with the single measles variety. The only significant association for being vaccinated before the onset of symptoms was found for the difference between MMR vaccination and nonvaccination.

Odds ratios did not change substantially after adjusting for potential confounders (eg, mother's age, medication during pregnancy, gestation time, perinatal injury, and 5-minute Apgar scale scores) (Table 4). Vaccination before diagnosis, regardless of vaccine variety used, significantly decreased the probability of being diagnosed with autism. Children vaccinated with MMR had a lower odds ratio of having autism than nonvaccinated children as well as those vaccinated with the single measles vaccine. After adjusting for potential confounders, the association between being vaccinated before the onset of symptoms and type of vaccine used became significant. The risk of having autism in children vaccinated with MMR was only 44% comparing to children vaccinated only against measles.

All models fit the data (likelihood ratio χ^2, P values mostly <0.0001, the larger one equals 0.0013).

DISCUSSION

Our study revealed that MMR vaccination was not significantly associated with an increased risk of autism in children. In a separate analysis, a similar result was achieved for the single-antigen measles vaccine. An unexpected finding was that odds ratios associated with MMR were lower than with the single measles vaccine.

Our results argue against the Wakefield et al hypothesis,[1] which suggested that developmental symptoms in children with autism may be triggered by the presence of the measles virus in the bowels of children vaccinated with MMR. He stated that the simultaneous administration of 3 types of live viruses in the MMR vaccine was too great a burden for a child's immunologic system, increasing the chance of measles virus persistence, subsequently leading to the development of autistic symptoms. Therefore in many countries, the increased incidence of childhood autism was initially linked with the launching of MMR vaccination campaigns. This study was unable to confirm the Wakefield et al hypothesis, finding a lower risk of developing autism for children vaccinated against measles, with the lowest risk being found for children vaccinated with MMR. Our study participants were not evaluated for the presence of the measles virus in their gastrointestinal tracts. Other previously published study found strong evidence against the association of autism with persistent measles virus RNA in gastrointestinal tracts exposed to the MMR vaccine.[14]

The findings of our study concerning the single-antigen measles vaccine cannot be compared with other reports, as no similar study has been previously published. Other studies examined sample populations vaccinated exclusively with MMR, as the triple vaccine program was launched much earlier in those countries, than in Poland. Yet this study was still able to reach conclusions similar to previously published studies, confirming that MMR is not associated with an increased risk of autism. Odds ratios obtained in this study were similar to those obtained by other authors.[15–17]

The decreased risk of autism among vaccinated children may be due to some other confounding factors in their health status. For example, healthcare workers or parents may have noticed signs of developmental delay or disease before the actual autism diagnosis and for this reason have avoided vaccination.

A heterogeneous population of children vaccinated with MMR or exclusively against measles is a strength of our study. First, such a study population offers the opportunity to evaluate those vaccinated with MMR and the single measles variety for the risk of autism. Second, it allowed for examining whether the risk of being diagnosed with autism differed between these 2 vaccines.

Participants' vaccination histories were taken directly from physician's records, eliminating the potential for recall bias. Because they are surveyed by independent public health workers at least twice per year, Polish vaccination records are very reliable.

Introducing the MMR vaccine as a replacement for the single-antigen measles vaccine in the mandatory vaccination schedule improved vaccination coverage against measles in Poland. This serves as evidence that, despite extensive media coverage of the debated association between MMR and autism, public acceptance of this vaccine remains very high. The situation in Poland is different to that of many European countries, where MMR vaccinations by age 2 years fell more than 10% and were followed by measles outbreaks. In this time, Poland's already high rate of measles immunization even slightly increased.[10]

We were able to control many potential confounding factors, known to be associated with vaccination practices and possibly serving as risk factors for autism. We included 2 index dates to assess previous vaccination: the onset of symptoms and of diagnosis of autism. Parental concern in regards to symptoms and symptom etiology, reported retrospectively, can be biased by confounding factors. Date of diagnosis based on physician's records is not affected by recall bias, serving as a better index date than the onset of symptoms.

One limitation of this study included omitting other pervasive developmental disorders. The decision was made to restrict the study population to cases of autism in the interest of better

examining possible associations connected only with this disease, the most severe of all autistic spectrum disorders. Still, this study had the possibility of comparing its findings with the results of other authors, who assessed the risk of autism in addition to other autistic spectrum disorders.[18–20]

The findings in this study may be useful in discussing the potential risks and benefits of vaccination programs which use the single versus triple MMR vaccine. These findings suggest that both vaccines are characterized by a similar level of safety with respect to the risk of autism in children.

REFERENCES

1. Wakefield A, Murch S, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 1998;351:637–641.
2. Berger A. The third degree MMR: can you decide? *Br Med J*. 2003;327:628.
3. Jackson T. MMR: more scrutiny, please. *Br Med J*. 2003;326:1272–1273.
4. Casiday R, Cresswel T, Wilson D, et al. A survey of UK parental attitudes to the MMR vaccine and trust in medical authority. *Vaccine*. 2006;24:177–184.
5. Madsen K, Hviid A, Vestergaard M, et al. A population based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med*. 2002;347:1477–1485.
6. Hendrickson B, Turner J. MMR vaccination, ileal lymphoid nodular hyperplasia, and pervasive developmental disorder. *Lancet*. 2002;359:2052–2053.
7. Maldonado Y. Current controversies in vaccination: vaccine safety. *JAMA*. 2002;288:3155–3158.
8. Wilson K, Mills E, Ross C, et al. Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: a systematic review of current epidemiological evidence. *Arch Pediatr Adolesc Med*. 2003;157:628–635.
9. DeStefano F, Karapurkar T, Thompson W, et al. Age of first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. *Pediatrics*. 2004;111:259–266.
10. Mrożek-Budzyn D, Kiełtyka A. The relationship between MMR vaccination level and the number of new cases of autism in children [in Polish]. *Przegl Epidemiol*. 2008;62:597–604.
11. Mayor S. Researcher from study alleging link between MMR and autism warns of measles epidemic. *Br Med J*. 2003;327:1069.
12. DeStefano F, Thompson W. MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines*. 2004;3:19–22.
13. Andrews N, Miller E, Taylor B, et al. Recall bias, MMR and autism. *Arch Dis Child*. 2002;87:493–495.
14. Horning M, Briese T, Buise T, et al. Lack of association between measles virus vaccine and autism with enteropathy: a case-control study. *PLoS One*. 2008;3:e3140.
15. Klein K, Diehl E. Relationship between MMR vaccine and autism. *Ann Pharmacother*. 2004;38:1297–1300.
16. Chen W, Landau S, Sham P, et al. No evidence for links between autism, MMR and measles virus. *Psychol Med*. 2004;34:543–553.
17. Uchigama T, Kurosawa M, Inaba Y. MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan. *J Autism Dev Disord*. 2007;37:210–217.
18. Smeeth L, Cook C, Fombonne E, et al. MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet*. 2004;364:963–970.
19. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry*. 2005;46:572–579.
20. Hopkins Tanne J. MMR vaccine is not linked with autism, says Danish study. *Br Med J*. 2002;325:1134–1140.

CURRENT ABSTRACTS

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Imported Case of Marburg Hemorrhagic Fever—Colorado, 2008

Centers for Disease Control and Prevention. *MMWR*. 2009;58:1377–1380.

A 44-year-old woman was hospitalized with an unexpected febrile illness in Colorado in January 2008 after returning to the United States from a 2-week safari in Uganda. Her hospital course was characterized by hepatitis, renal failure, pancytopenia, coagulopathy, myositis, pancreatitis, and encephalopathy. Testing was negative for leptospirosis, viral hepatitis, malaria, arboviral infection, acute schistosomiasis, rickettsial infection, and viral hemorrhagic fevers (VHF), including Ebola and Marburg hemorrhagic fever (MHF).

In July 2008, the patient requested repeat testing after she learned of the fatal case of MHF in a Dutch tourist who recently had visited the same cave she had visited in Uganda, the Python Cave. Serum collected 6 months after the Colorado patient's illness tested positive for anti-Marburg virus IgG by ELISA, prompting additional testing of archived day 10 serum. Nested RT-PCR confirmed the presence of Marburg virus RNA fragments in the day 10 sample.

Comment: Before the case described in this report, the only human cases of VHF imported into the US were single cases of Lassa fever in Chicago in 1989, and in Trenton in 2004. No previous cases of imported filovirus (Marburg or Ebola virus) have been reported in the US, making this the first imported case of a filoviral hemorrhagic fever in the US.

Growing evidence demonstrates that fruit bats are the natural reservoir of Marburg virus. The patient may have acquired Marburg virus infection through exposure to bat secretions or excretions while visiting the Python Cave. Although the Python Cave is closed and no additional MHF cases have been reported, travelers should be aware of the risk for acquiring MHF in endemic areas in Africa and should avoid entering caves or mines inhabited by bats in these areas.

Health-care providers should have a low threshold of suspicion for VHF among travelers returning from endemic areas, promptly implement appropriate infection control measures, and rapidly report suspected cases, which are nationally notifiable.