

## Response to Measles-Mumps-Rubella Vaccine in Children with Autism Spectrum Disorders

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**Abstract.** *Background/Aim: The etiology of autism spectrum disorders (ASD) is unknown. The measles-mumps-rubella (MMR) vaccination has been in the past implicated in ASD pathogenesis. The aim of our study was to evaluate the rate of seropositivity and the levels of antibodies against MMR antigens in a cohort of children with ASD compared to control children. Patients and Methods: In a cohort of children with ASD and same-age healthy controls, we measured levels and seropositivity of antibodies against MMR. Results: A total of 60 children, 31 with ASD and 29 controls were enrolled. The seropositivity rate and levels of all the three antibodies were similar in cases and controls. Conclusion: Children with ASD have a similar level and seropositivity rate of antibodies against the MMR vaccine to same-age controls. As persistent infections are typically associated with high antibody levels, our results support the arguments against a role of MMR vaccination as a causal factor or co-factor in development of ASD.*

Autism spectrum disorders (ASD) are behaviorally-defined as developmental disorders of the central nervous system characterized by impairments in communication and social reciprocity, complemented by limited, repetitive interests and behaviors (1). Currently, the ASD category includes autistic disorder (also called "classic" autism), Asperger syndrome, pervasive developmental disorder, not otherwise specified (or atypical autism), childhood disintegrative disorder and Rett syndrome.

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Autistic disorder is the most severe form of ASD. Abnormalities usually appear before three years of age. In some cases, its onset is delayed (the so-called "regressive form"). Atypical autism is a pervasive developmental disorder that differs from autism in terms, either of age of onset, or of failure to fulfill all three sets of diagnostic criteria.

The etiology of ASD is unknown, although both genetic and environmental factors play a causative role (2-4). One of the most mysterious features of ASD is the increase in the number of diagnoses in recent decades (5-9). In fact, before the 1980s, a prevalence of 1:2,000 children was estimated (8), whereas a recent survey indicates dramatically higher figures (1:110 US children) (9). It has yet to be established whether this increase represents an actual change in numbers, a simple effect of improved diagnostic means, or a combination of both (10).

Among other factors, the measles-mumps-rubella vaccine has been implicated in ASD etiology and in the increase of its prevalence rate in an article which was later retracted (11). To explore this issue, several research groups have investigated the levels of antibodies against measles (12, 13) or against measles-mumps-rubella antigens (1, 14, 15) in children with ASD compared to healthy ones. Results were conflicting. Higher levels of some (or all) of these antibodies in children with autism, compared to healthy controls have been reported (14, 15), whereas in other studies, no difference was detected (1, 12, 13). Interestingly, some groups observed a significantly higher rate of seronegativity to MMR vaccine in patients with autistic disorder *versus* their healthy siblings (16).

The aim of our study was to evaluate the seropositivity rate and the antibody titers against MMR antigens in a cohort of children with ASD compared to a cohort of controls, enrolled in a Division of Pediatric Surgery.

## Patients and Methods

**Patients.** We enrolled patients admitted as in- or out-patients to the services of Child and Adolescent Neuropsychiatry Unit at the Second University of Naples and to the Clinical of Pediatrics of “Federico II” University, Italy, between January 2010 and June 2011. Consent forms were obtained from the children’s parents/legal guardians, and the study was approved by the Ethics Committee of University of Naples “Federico II” (protocol number: 85/09). Inclusion criteria for cases were: diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision (DSM-IV-TR) (17); informed consent signed by parents/guardians; and information regarding vaccinations. There was only one exclusion criterion, namely the inability to sign an informed consent form. Controls were recruited at the Division of Pediatric Surgery where they were admitted for minor surgical treatments (e.g. phimosis, hernias, etc.). Controls underwent an interview to rule-out possible ASD. If such a disorder was identified, the child was excluded from the study.

Cases were administered the Autism Diagnostic Interview, Revised version (18), the Childhood Autism Rating Scales (CARS) (19) and the Autism Diagnostic Observation Schedule (ADOS)-Generic (20) to verify the diagnosis of autism. Adaptive functioning was assessed with the Vineland Adaptive Behavior Scales (21). Developmental quotient was determined by the Griffith Mental Developmental Scales (22).

**Virological tests.** Anti-measles IgG antibodies were detected using an enzyme-linked immunosorbent assay (ELISA) (Enzygnost method; Siemens Healthcare Diagnostics, Marburg, Germany). In detail, each blood specimen was divided into two aliquots, a first one placed in the left well and a second one in the right well. The wells in the left row of each strip were coated with antigen derived from permanent simian kidney cells infected with measles virus, and the wells in the right row were coated with antigen from non-infected cells (control antigen). For each sample, the cut-off index (COI) was calculated by the following formula: (optical density (OD) of left well – OD of right well)/0.220. Samples with COI >1 were considered positive.

Anti-mumps IgG antibodies were detected by a different ELISA technique (RADIM S.p.a., Pomezia, Italy).

For each sample, the COI was calculated by dividing the OD of the sample by 0.59. Samples with COI >1 were considered positive.

Specific IgG against Rubella virus were identified using an antibody capture chemiluminescence immunoassay (DiaSorin, Saluggia, Italy) and an automated instrument (LIASON, DiaSorin, Saluggia, Italy).

Results are given in IU/ml, according to the manufacturer’s instructions. Samples with titers >11 IU/ml were considered positive.

**Statistical analysis.** The Kolmogorov-Smirnov test was used to check for quantitative variables for Gaussian distribution. In the case of Gaussian distribution, data are reported as the mean±standard deviation (SD), while in cases of non-Gaussian distribution, they are reported as median and interquartile range (IQR). In cases of Gaussian distribution, the Student’s *t*-test for unpaired variables was applied, while the Mann-Whitney *U*-test was used in cases of non-Gaussian distribution. For comparisons among more than two groups (controls, AD, and non-AD ASD), an ANOVA test or the Kruskal-Wallis test were applied in case of Gaussian or non-

Table I. Demographic and clinical features of children with Autism Spectrum Disorders (n=31).

Type of disease	
AD	14 (45.2%)
Non-AD ASD	17 (54.8%)
Head circumference (cm)	51.95 (48.00-53.08)
Height (cm)	121 (106.75-134.90)
Weight (kg)	26.40 (20.12-33.25)
GMD5 (Developmental Quotient)	49 (38.25-57.50)
VABS (Adaptive Quotient)	49 (36.50-57.25)
ADOS (Total Score)	16.5 (14-18)
CARS (Total Score)	37.5 (34-40)

Data are reported as number (percentage) for qualitative variables and as median (interquartile range) for quantitative variables. GMD5: Griffith Mental Developmental Scales; VABS: Vineland Adaptive Behavior Scales; ADOS: Autism Diagnostic Observation Schedule; CARS: Childhood Autism Rating Scales; AD: autistic disorder.

Gaussian distribution, respectively. As age may significantly impact on antibody titer (1), a generalized linear model (GLM) was used to correct antibody titer for age and sex. The  $\chi^2$  test with Yates correction (or Fisher’s exact test where appropriate) was used for categorical variables. For more than two variables, a higher value of 99% confidence interval of the Monte Carlo estimation of Fisher’s exact test was used instead of Fisher’s exact test. Spearman’s rho test was used for correlations between continuous variables. A *p*-value of 0.05 or less in the two-sided test was considered statistically significant. Logistic regression analysis was used to correct seropositivity rate for age and sex. All statistical analyses were carried out using the Statistical Package for the Social Sciences version 18.0 (SPSS Inc. Chicago, IL, USA).

## Results

We enrolled 60 children in the study, 31 with ASD and 29 controls. None of the controls was found to be affected by a neuropsychiatric disorder. All participants underwent vaccination against MMR according to the Italian schedule, which requires a first dose at the age of 12-14 months and a second one at the age of 5-6 years. The median age was 5.75 years for study cases (IQR=3.17-8.38 years) and 5.75 for controls (IQR=4.21-8.19 years) (*p*=0.750). Males outnumbered females, both among cases (26/31, 83.9%) and controls (25/29, 86.2%, *p*=0.999). The demographic and clinical features of the 31 children with ASD are shown in Table I.

We assessed the rate of seropositivity against MMR antigens and compared this rate between cases and controls. As shown in Table II, the rate of seropositivity was similar in cases and controls. Logistic regression analysis showed that neither age nor gender affected the seropositivity status in relation to the three antibodies. We measured and compared antibody titers against Rubella in cases and controls using a commercial quantitative chemiluminescence assay. To

Table II. Rate of seropositivity to Measles-Mumps-Rubella vaccine antigens in cases and controls and in Autistic Disorder and non-Autistic Disorder Autism Spectrum Disorders.

Seropositivity against	Cases		Controls	p-Value
Measles virus	26/30 (86.7%)	AD 12/14 (85.7%) Non-AD ASD 14/16 (87.5%)	22/28 (78.6%)	0.499 (F) <sup>†</sup> 0.751 (FM) <sup>‡</sup>
Mumps virus	11/30 (36.7%)	AD 2/13 (15.4%) Non-AD ASD 9/17 (52.9%)	6/29 (20.7%)	0.176 ( $\chi$ ) <sup>†</sup> 0.054 (FM) <sup>‡</sup>
Rubella virus	25/29 (86.2%)	AD 11/13 (84.6%) Non-AD ASD 14/16 (87.5%)	26/29 (89.7%)	0.999 (F) <sup>†</sup> 0.085 (FM) <sup>‡</sup>

$\chi$ :  $\chi^2$  test; F: Fisher's exact test; FM: Fisher's exact test (Monte Carlo estimation); <sup>†</sup>Cases vs. controls; <sup>‡</sup>AD vs. non-AD ASD vs. controls.

Table III. Titer of antibodies against rubella and cut-off values obtained testing mumps and measles antibodies in cases and controls and in Autistic Disorder and non-Autistic Disorder Autism Spectrum Disorders.

	Cases	Controls	p-Value
Measles virus antigens (COI)	2.62 (1.37-3.18) N=30	AD 2.62 (1.57-3.10) n=14 Non-AD ASD 2.62 (1.22-3.74) n=16	2.23 (1.10-4.22) N=28 0.950 (U) <sup>†</sup> 0.996 (K) <sup>‡</sup>
Mumps virus antigens (COI)	0.79 (0.39-1.51) n=30	AD 0.50 (0.18-0.87) n=13 Non-AD ASD 1.09 (0.47-1.60) n=17	0.77 (0.37-0.95) n=29 0.544 (U) <sup>†</sup> 0.112 (K) <sup>‡</sup>
Rubella virus antigens (IU/ml)	32.70 (19.10-74.25) n=29	AD 31.2 (12.85-89.20) n=13 Non-AD ASD 42.55 (28.03-75.18) n=16	50.80 (27.25-104.75) n=29 0.287 (U) <sup>†</sup> 0.469 (K) <sup>‡</sup>

Data are given as median (interquartile range). K: Kruskal-Wallis test; U: Mann-Whitney *U*-test; <sup>†</sup>Cases vs. controls; <sup>‡</sup>AD vs. non-AD ASD vs. controls.

measure measles and mumps antibody titers, standard commercial qualitative ELISA's assays were used. COI values are reported in Table III. Although COI values cannot be considered strictly a titer, the data obtained are indicative of antibody concentrations.

As shown in Table III, antibody titers against MMR did not differ between cases and controls. The GLM revealed that neither age nor gender affected the titers of the three antibodies.

Moreover, we evaluated the titers and seropositivity rate of the antibodies against MMR antigens in controls, and in the children with AD and non-AD ASD. As shown in Table II and III, neither seropositivity rate nor antibody titers against MMR antigens were significantly different among these three groups.

We correlated severity scores *i.e.* ADOS (20) and CARS (19) scores with antibody titer by the mean of the Spearman's rho test.

For ADOS,  $\rho$  was 0.100 ( $p=0.958$ ), -0.248 ( $p=0.186$ ), and 0.139 ( $p=0.471$ ) for antibodies to measles, mumps and rubella, respectively. The corresponding figures for CARS were -0.006 ( $p=0.977$ ), 0.079 ( $p=0.679$ ), and 0.044 ( $p=0.820$ ). Moreover, the median values of these scales did not differ between seropositive and seronegative patients in relation to the three antibodies tested. In detail, for measles

antibodies, the median ADOS score was 16 (IQR=14-17.25) for seropositive and 15 (IQR=11.25-18) for seronegative children ( $p=0.877$ ) and the median CARS score was 38 (IQR=34-40.5) for seropositive and 37 (IQR=31-41.5) for seronegative children ( $p=0.668$ ). For mumps antibodies, the median ADOS score was 15 (IQR=12-17) for seropositive and 17 (IQR=16-18) for seronegative children ( $p=0.079$ ), and the median CARS score was 38 (IQR=34-40) for seropositive and 37 (IQR=33-42) for seronegative children ( $p=0.665$ ). For rubella antibodies, the median ADOS score was 17 (IQR=14-18) for seropositive and 14 (IQR=11.25-16) for seronegative children ( $p=0.133$ ) and the CARS score was 37 (IQR=34-40) for seropositive and 40 (IQR=32.5-43.75) for seronegative children ( $p=0.504$ ).

Hence, the level of behavioral, communicative, social and intellectual impairment did not correlate with antibody titer or seropositivity status.

## Discussion

Despite research, the etiology of ASD and the increase of its prevalence remains an unsolved issue. In 1998, Wakefield *et al.* reported 12 patients with an inflammatory bowel condition and regressive developmental disorders (11). They hypothesized that the MMR vaccine could trigger bowel dysfunction which

subsequently resulted in neurodevelopmental disorders *via* gastrointestinal absorption of toxic neuropeptides involved in central nervous system damage. This speculative, and then retracted article, led to a decline in parental confidence in public health vaccination programs and therefore in MMR vaccination rates, which in turn, resulted in outbreaks of measles infection (23-26). Interestingly, there is a general consensus that autism is a disorder occurring in early embryonic development. This basic consideration argues against any role of a vaccination given after birth (26). A theoretic biological plausibility persists for cases with regression onset (26), even if they are considered intrauterine-life disorders by some other authors (27).

The claimed mechanism for the MMR and autism association are: i) the induction by viral antigens of antibodies that cross-react with host tissues, or ii) persistent infection by the attenuated viruses contained in the vaccine (1). Regarding the first mechanism, cross-reactivity between measles virus and myelin basic protein (MBP) has been proposed (12, 14, 28). However, several authors failed to find evidence of cross-reactivity of autoantibodies against MBP and measles virus (29-32), and of chicken MBP residues in commercially available MMR vaccine (33). With respect to the second mechanism, levels of antibodies against measles or against the MMR vaccine have been found to be higher in children with ASD compared to healthy controls (14, 15), thereby providing a biological corroboration for the association between MMR vaccine and ASD. In fact, in a typical persistent infection by measles virus, such as subacute sclerosing panencephalitis, very high titers of measles antibodies are found both in serum and in cerebral spinal fluid (34, 35). Instead, in our study, which as far as we are aware, is the first to be devoted to MMR vaccine and ASD performed in Italy, we found no difference in seropositivity rate or in antibody titer between children with ASD and same-age controls. Moreover, among cases, there was no difference in the titer of antibodies against MMR between AD and slighter forms of ASD.

These findings are consistent with previous studies (1, 12, 13) and strongly argue against persistent infection by measles, mumps or rubella virus in children with ASD.

A potential limitation of our study is the relatively small sample size. However, the number of subjects enrolled is comparable to that of previous similar studies (1, 15). Moreover, the difference we found in the antibody titers and in the seropositivity rates between cases and controls is so low that a type-II error seems unlikely to have occurred.

Our study provides a very carefully evaluated group of control subjects. On the contrary, in other protocols (15, 16), siblings were recruited as controls and this choice may constitute a major limitation because of the well-known role of genetic factors in the etiology of ASD. Moreover, most studies on this topic (12, 15) did not perform a separate analysis based on disease severity.

The lack of difference emerging from our study in seroprevalence and antibody titer between controls and cases and the absence of correlation between antibody titers and severity of the disorder assessed *via* behavioral and cognitive scales strengthen our conclusions.

Many epidemiological studies similarly failed to find an association between MMR immunization and autism (10, 36-47). In particular, Taylor *et al.* evaluated the change in incidence of ASD in a London district between 1979 and 1998, and related the data to the regional vaccination registry (36). They found a steady increase in the incidence of ASD after 1979, but no “step-up” effect after the introduction of MMR vaccination in 1988. They also observed no difference in age of onset in cases vaccinated before or after 18 months of age, or in those not vaccinated, neither was there a temporal association between the onset of ASD within one or two years after vaccination with MMR. The authors stated that ASD was not associated with MMR vaccination (36).

In conclusion, children with ASD have a similar titer and seropositivity rate of antibodies against MMR vaccine antigens to same-age controls. This constitutes a strong argument against a role of MMR vaccination as a causal factor or co-factor of ASD, supporting data from other epidemiological studies.

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