

# Association of Autistic Spectrum Disorder and the Measles, Mumps, and Rubella Vaccine

## A Systematic Review of Current Epidemiological Evidence

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**Objective:** To systematically review the evidence for and against the existence of an association between autistic spectrum disorder (ASD) and the measles, mumps, and rubella (MMR) vaccine.

**Study Design:** We conducted a systematic review of the medical literature to identify all controlled epidemiological articles examining for an association between ASD and the MMR vaccine. We extracted data from the articles on the characteristics and objectives of the study as well as evidence of an association.

**Results:** Twelve articles met the inclusion criteria. One study found no difference in the rates of ASD and the MMR vaccine in children who were vaccinated and those who were not. Six studies examined for evidence of an increase in ASD associated with an increase in the MMR vaccine coverage, none of which showed evidence of an association. Four studies examined if a variant form of ASD was

associated with the MMR vaccine, none of which showed evidence of an association. Eight studies attempted to determine if there was a temporal association between developing ASD and receiving the MMR vaccine. Of these, 1 study identified an increase in parental concern in the 6-month period following vaccination with MMR in one of its analyses. The results of all other studies showed no association between ASD and the MMR vaccine.

**Conclusions:** The current literature does not suggest an association between ASD and the MMR vaccine; however, limited epidemiological evidence exists to rule out a link between a rare variant form of ASD and the MMR vaccine. Given the real risks of not vaccinating and that the risks and existence of variant ASD remain theoretical, current policies should continue to advocate the use of the MMR vaccine.

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**I**N 1998 Wakefield et al<sup>1</sup> published a description of 12 cases of pervasive developmental delay associated with gastrointestinal (GI) tract symptoms and developmental regression, many of who reported soon after the patient received a measles, mumps, and rubella (MMR) vaccination. This case series puts forth the hypothesis that a new variant of autistic spectrum disorder (ASD) was developing and was associated with the MMR vaccine. Although the study was heavily criticized for its methods, it created widespread concern among the public about the safety of the MMR vaccine.<sup>2</sup> Despite government assurances, MMR vaccination rates have decreased in the United Kingdom resulting in measles outbreaks.<sup>3</sup> In response to the growing public concern, several epidemiological studies have been conducted to examine the association between ASD and the MMR vaccine. These studies have been designed to address several hypotheses put forth by the study of Wakefield et al and others that have

cautioned against the use of the MMR vaccine. The specific hypotheses that have been examined are (1) rates of ASD are higher in individuals who have received the MMR vaccine than in those who have not, (2) an increase in ASD may be occurring as a consequence of the MMR vaccine, (3) the development of ASD is temporally associated

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with receiving the MMR vaccine, and (4) a new variant form of ASD may be associated with the MMR vaccine. In this article we systematically identify, summarize, and present the results of these studies.

## METHODS

### LITERATURE SEARCH

We conducted a search of English and non-English language articles in the following databases: CINAHL (1982- February 2003), PsychINFO (1872-January 2003), MEDLINE

(1966-Jan 2, 2003), PreMedline (end of January 2003), TOXLINE (1966-Jan 2003), Biological Abstracts (1990-December 2002), EMBASE (1982-Week 6, 2003), The Cochrane Library (to the fourth quarter of 2002), and HealthSTAR (1975-December 2002). We first searched for articles on the MMR vaccine beginning with the controlled vocabulary term “measles-mumps-rubella vaccine” (or a similar term depending on the database being searched) combined with a search of the title and abstract fields using “mumps measles rubella vaccin\$,” “MMR vaccin\$,” “measles, mumps, rubella vaccin\$,” and other similar terms. We next searched for articles on ASD using the controlled vocabulary term “autistic disorder” (or a similar term depending on the database being searched) combined with a search of the title and abstract fields using “autism,” “autistic disorder,” and “autistic spectrum disorder.” The MMR vaccine and the ASD searches were combined with the Boolean Operator “and.” To supplement this search, we also contacted authors of published studies and searched the bibliographies of reviews.<sup>4,6</sup>

### SELECTION OF ARTICLES

We independently searched the databases in duplicate and identified relevant abstracts. We reviewed the articles associated with these abstracts and selected final articles for inclusion in the systematic review. To be included in our final review a manuscript had to (1) report the results of an original epidemiological study, (2) describe a systematic method of identifying a sample (eg, analysis of ASD registry), (3) describe methods by which the diagnosis of ASD was established, and (4) attempt to determine if an association existed between MMR vaccination and ASD. Any disputes on inclusion criteria of either abstracts or final articles were resolved by consensus and, if necessary, a third reviewer was consulted.

### DATA EXTRACTION

In duplicate, we extracted data from the articles on the following: characteristics of the study—first author, journal, year of publication, country of study, study design, type and size of population studied, age of MMR vaccination, and method of ASD diagnosis; and study results—type of association tested (comparison of rates of ASD in children receiving the MMR vaccine and those who did not, change in rates of ASD associated with changes in MMR, temporal association of ASD with MMR, association of variant ASD with MMR), method of analysis, and results of analysis. Any disagreements between the data extractors were resolved by discussion until consensus was achieved. If manuscripts contained several analyses, we extracted data only on those analyses that met our inclusion criteria. We classified results of the study by the type of association tested. If some articles carried more than one type of analysis, we included these results in each relevant category.

## RESULTS

### SEARCH RESULTS

We screened a total of 379 abstracts of potentially eligible articles. Of these abstracts we included 20 studies for additional analysis. We excluded 10 studies that did not meet our inclusion criteria for a variety of reasons including not having yet been completed,<sup>7</sup> examining only for a link between the MMR vaccine and pathologic features of the GI tract,<sup>8</sup> examining for a link between maternal MMR vaccination and development of ASD,<sup>9</sup> or only examining for biological evidence of a link between ASD and the

MMR vaccine.<sup>10</sup> One letter did examine directly for a link between ASD and the MMR vaccine but was not reported in sufficient detail to be included.<sup>11</sup> We also identified an additional 2 articles from references of reviews.<sup>12,13</sup> A final total of 12 articles were found to meet our inclusion criteria and were included in this systematic review.<sup>12-23</sup>

### CHARACTERISTICS OF STUDIES

The 12 studies included in the systematic review were conducted in 5 different countries (**Table 1**). Data were obtained from populations born as far back as 1954.<sup>20</sup> Three studies relied on the same data source<sup>15,16,21</sup> and another 2 studies also shared data sources<sup>13,14</sup> leaving a total of 9 distinct sources of data examined. The studies varied in design and included case series, time-series analyses, cross-sectional study designs, self-matched case series, and retrospective cohort studies. Studies varied in how ASD was diagnosed with most relying on the records of services for autistic children or children with disabilities or *International Classification of Diseases* codes. The 3 studies that provided data on the age of the child when they received the vaccination suggested that the initial MMR vaccination was received at ages 13 through 17 months.<sup>15,18,20,22</sup>

#### Hypothesis 1

*Autistic spectrum disorder rates are higher in individuals who received the MMR vaccine compared with those who have not been vaccinated.*

Only 1 study examined the rates of ASD in MMR vaccinated and not vaccinated individuals in the same period.<sup>22</sup> This study, a retrospective cohort of children in Denmark, identified no statistically significant differences in rates of autism or ASD between these 2 populations in adjusted and nonadjusted analyses (**Table 2**).

#### Hypothesis 2

*Increasing rates of ASD are occurring as a consequence of the MMR vaccine.*

Six studies examined to see if there was an association between changes in the rate of ASD and changes in the level of the MMR vaccine coverage (**Table 3**).<sup>12,15,17,18,20,21</sup> These analyses were conducted in the United Kingdom, Sweden, and the United States. Of these, 4 studies conducted time-series analyses, none of which identified an obvious association between an increase in ASD or variant ASD and equivalent increase in the MMR vaccine coverage.<sup>15,17,18,21</sup> One of the remaining 2 studies looked at the numbers of cases of ASD before and after MMR vaccination programs were introduced and did not find an increase in ASD rates in the period of MMR vaccination.<sup>12</sup> The other study compared rates of developmental regression in a sample of autistic children before the MMR vaccine was introduced and after it was introduced and found no significant differences.<sup>20</sup>

#### Hypothesis 3

*Development of ASD is temporally associated with receiving the MMR vaccine.*

**Table 1. Characteristics of Studies**

Source	Country	Population*	Mechanism of ASD Diagnosis
Gillberg and Heijbel, <sup>12</sup> 1998	Sweden	Population study of children, born between 1975 and 1984, diagnosed as having ASD in Goteberg and Bohuslan, Sweden (N = 55)	Diagnosis of <i>DSM III-R</i> autistic disorder by team of experts
Patja et al, <sup>13</sup> 2000†	Finland	All children receiving MMR vaccinations between 1982 and 1996 (about 1.8 million vaccinees)	Passive reporting of adverse events to National Public Health Institute Report by health care providers
Peltola et al, <sup>14</sup> 1998	Finland	31 Children reported to have developed GI tract symptoms after having received an MMR vaccination	Based on review of hospital or health center records or interviewed public health nurses (mean of 9 y 3 mo after GI tract symptoms developed)
Taylor et al, <sup>15</sup> 1999	UK	Children younger than 16 years, born from 1979 to mid 1998, with ASDs in 8 health districts (498 children with ASD: 261 with core ASD, 166 with atypical ASD, 71 with Asperger syndrome)	Computerized, special needs or disability registers at child development centers, records in special schools (checked by pediatric registrars using <i>ICD 10</i> classification)
Farrington et al, <sup>16</sup> 2001‡	UK	Extended analysis of Taylor et al <sup>15</sup> (n = 357 for diagnosis of ASD, 326 for parental concern, and 105 for regression)	Child development centers and special schools (checked by pediatric registrars using <i>ICD 10</i> classification)
Dales et al, <sup>17</sup> 2001	USA	Statewide surveys (California): Random samples of kindergarten pupils, immunization records at age 24 mo born between 1980 and 1994 (600-1900/y)	ASD caseload of department of Developmental Services Regional Centers for persons with disabilities ( <i>ICD 9</i> classification)
Kaye et al, <sup>18</sup> 2001	UK	Consecutive annual birth cohorts of autistic boys born during 1988-1993 (114 autistic boys, aged 2-5 y)	UK General Practice Database (general practitioner diagnosis with 81% referred to specialists)
DeWilde et al, <sup>19</sup> 2001	UK	71 Children with ASD, 284 matched controls; identified from UK General Practice Database between 1989 and 2000	General practitioner diagnosis
Fombonne and Chakrabarti, <sup>20</sup> 2001	UK	(1) Epidemiological sample of 96 children with pervasive developmental disorder born between 1992 and 1995 (after introduction of MMR vaccine) (2) After introduction of MMR vaccine, clinical sample of 68 autistic children born between 1987 and 1996 (3) Before introduction of MMR vaccine, clinical sample of 98 autistic children born between 1954 and 1979	Autism diagnostic interview-revised and <i>ICD-10/DSM-IV</i> diagnoses
Taylor et al, <sup>21</sup> 2002‡	UK	Children younger than 16 y, born from 1979 to mid 1998, with ASDs in 8 health districts (473 children with autism: 278 with core autism, and 195 with atypical autism)	Computerized, special needs/disability registers at child development centers, records in special schools, child psychiatric records (checked by pediatric registrars using <i>ICD 10</i> classification)
Madsen et al, <sup>22</sup> 2002	Denmark	All children born between January 1991 and December 1998 and registered in Danish Civil Registration system; vaccination data based on general practitioners' reports to National Board of Health	All diagnoses in hospitals and outpatient clinics based on <i>ICD 10</i> codes were identified from Danish Psychiatric Central Register; 40 charts reviewed by child psychiatrist for confirmation.
Makela et al, <sup>23</sup> 2002	Finland	535 544 Vaccinees aged 1 to 7 y enrolled in surveillance study between November 1982 and June 1986	Hospitalizations for autism based on <i>ICD 8</i> or <i>9</i> codes from nationwide hospital register between November 1982 and December 1995

Abbreviations: ASD, autistic spectrum disorder; *DSM III-R*, *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*; *DSM IV*, *Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition*; GI, gastrointestinal; *ICD*, *International Classification of Diseases*; MMR, measles-mumps-rubella; UK, United Kingdom; USA, United States of America.

\*This is the population studied for analysis data that we extracted.

†Same data set as Peltola et al<sup>14</sup> was used.

‡Same data set as Taylor et al<sup>15</sup> was used.

**Table 2. Comparison of Rates of Autistic Spectrum Disorder (ASD) in Vaccinated and Unvaccinated Individuals**

Source	Analysis	Results
Madsen et al, <sup>22</sup> 2002	Determined rates of autism and ASD in 440 655 vaccinated and 96 648 unvaccinated individuals; analysis was based on person-years of follow-up and was adjusted for several potential confounding variables	Adjusted RR of autism in vaccinated individuals, 0.92 (95% CI, 0.68-1.24); adjusted RR of ASD in vaccinated individuals, 0.83 (95% CI, 0.65-1.07)

Abbreviation: CI, confidence interval; RR, relative risk.

Eight studies examined for a temporal association between developing ASD and having received the MMR vaccine (**Table 4**).<sup>13,15,16,19-23</sup> Three of these studies compared the age at which ASD was diagnosed, or parental concern developed, in individuals who were vaccinated and those who were not vaccinated.<sup>15,20,22</sup> The hypothesis in these studies was that if the MMR vaccine caused ASD, populations exposed to the vaccine should develop ASD at a different age than populations who were not exposed to the vaccine. These studies, however, found no differences in the mean age at the time of diagnosis of ASD.

Six studies examined for an increased frequency of the diagnosis of ASD or evidence of features suggestive

**Table 3. Comparison of Changes in Rates of Autistic Spectrum Disorder (ASD) With Changes in Measles, Mumps, Rubella (MMR) Vaccine Coverage**

Source	Analysis	Results
Gillberg and Hejbel, <sup>12</sup> 1998	Case series: Compared proportions of autistic cases in high and low coverage periods	MMR: Coverage substantially increased in 1980s ASD: 62% of sample (34 children) born prior to increase in MMR vaccine coverage (55% of period); 38% of sample (21 children) born after increase (45% of sample)
Taylor et al, <sup>15</sup> 1999	Time series: Compared changes in rates of ASD in periods before and after MMR vaccine introduced	MMR: Introduced in 1987 ASD: No sudden step-up in cases of core and atypical autism in 1987 ( $P > .25$ ); no change in trend in ASD before and after 1987
Dales et al, <sup>17</sup> 2001	Time series: Compared increasing rates of ASD to increasing rates of MMR vaccine coverage (1980-1994 birth cohorts)	MMR: Increase in coverage from 72% to 82% (14% relative increase) ASD: Increase in ASD births from 44/100 000 to 208/100 000 (373% relative increase)
Kaye et al, <sup>18</sup> 2001	Time series: Compared increasing rates of ASD to changes in rates of MMR vaccine coverage	MMR: Rates stable at 97% ASD: Increase in cumulative incidence of ASD from 8/10 000 to 29/10 000 ( $P < .0001$ trend)
Fombonne and Chakrabarti, <sup>20</sup> 2001	Cross-sectional study: Compared rates of developmental regression in samples of autistic children before and after introduction of the MMR vaccine	Rate of any developmental regression reported in pre-MMR sample = 18.4% ( $P > .15$ ); in post-MMR sample = 15.6%
Taylor et al, <sup>21</sup> 2002	Time series: Determined if there was an increasing percentage of children with ASD and either GI tract symptoms or regression between 1979 and 1998	MMR: Introduced in October 1998 ASD: No trend in increasing percentages of children with ASD who had bowel symptoms (OR, 0.98; 95% CI, 0.93-1.04; $P = .50$ ) or who had regression (OR, 0.98; 95% CI, 0.93-1.03; $P = .47$ ) over entire period

Abbreviations: CI, confidence interval; GI, gastrointestinal; OR, odds ratio.

of ASD after children received the MMR vaccine. Of these, 1 study did not observe an increase in consultation rates to general practitioners following MMR vaccination in children later diagnosed as having autism, when compared with nonautistic control subjects.<sup>19</sup> One study, and an extended analysis of this study, examined a cohort of children with ASD and found that these children were not more likely to be diagnosed as having ASD, or identified as having developmental regression, in specified periods after having been vaccinated with the MMR vaccine.<sup>15,16</sup> An increased rate of parental concern was observed in the 6-month period following vaccination although this was not significant for any other period after MMR vaccination. One study compared the rates of parental concerns about bowel symptoms or regression among children who are autistic and who had received an MMR vaccination, children who are autistic before an MMR vaccination, and children who are autistic but were not vaccinated, and found no significant differences.<sup>21</sup> One study did not identify any cases of ASD in 1.8 million individuals who had received MMR vaccinations.<sup>13</sup> A Finnish study found no evidence of a clustering of hospitalizations for autism after children had received the MMR vaccine.<sup>23</sup> A Danish study of a population cohort who had received the MMR vaccine found no association between development of ASD and interval since vaccination.<sup>22</sup>

#### Hypothesis 4

*A new variant form of ASD may be associated with the MMR vaccine.*

Four studies attempted to examine for a specific association of a variant form of ASD with the MMR vac-

cine (**Table 5**).<sup>14,20,21,23</sup> Variant ASD was identified by the presence of developmental regression or GI tract symptoms. Of the 3 studies, 1 case series found that none of 31 children who developed GI tract symptoms after MMR vaccination subsequently went on to develop ASD.<sup>14</sup> One study did not find a difference in the rates of developmental regression in children with ASD in a sample of children after the introduction of the MMR vaccine to the population (post-MMR vaccination) when compared with a historical sample prior to the introduction of the MMR vaccine.<sup>20</sup> The study also did not find a higher than expected prevalence of childhood disintegrative disorder in the post-MMR vaccine sample. Another study did not find an increase in the percentages of children with autism who had GI tract symptoms or regression after the introduction of the MMR vaccine to that population.<sup>21</sup> Another study found that none of the 309 children who had received the MMR vaccine and had subsequently been hospitalized with autism had also been hospitalized with inflammatory bowel disease.<sup>23</sup>

#### COMMENT

The studies included in this review examined the hypotheses put forth by Wakefield et al.<sup>1</sup> None of the studies we examined provided evidence of an association between ASD and the MMR vaccine. Establishing whether associations exist between rare conditions and exposures is challenging, and the question of whether the MMR vaccine causes ASD is particularly difficult to answer for several reasons. The higher validity forms of observational studies such as controlled cohorts and case-control studies are of limited usefulness owing to the small numbers of individuals who are not vaccinated after MMR

**Table 4. Temporal Association of Autistic Spectrum Disorder (ASD) With Measles, Mumps, Rubella (MMR) Vaccine**

Source	Analysis	Results
Taylor et al, <sup>15</sup> 1999	Case series: Compared ages of ASD diagnosis in those vaccinated before 18 mo, after 18 mo, and those not vaccinated Self-matched case series: Compared rates of regression, parental concern, or diagnosis of ASD in specified periods after vaccination to all other periods for that individual	No significant difference in age at diagnosis among the 3 groups that were compared ( $P = .41$ ) No increased incidence of diagnosis of ASD or regression 6 mo and 1 y after vaccination; significant increased risk of parental concern 6 mo after vaccination ( $P = .03$ )
Patja et al, <sup>13</sup> 2000	Case series: Identified all reports of vaccine-related complications	No cases of postvaccination ASD (based on passive reporting) in about 1.8 million vaccinees
Farrington et al, <sup>16</sup> 2001	Self-matched case series: Compared rates of regression, parental concern or diagnosis of ASD in specified periods after vaccination to all other periods for that individual (Extended analysis of Taylor et al <sup>15</sup> )	No increased incidence of diagnosis of ASD, regression or parental concern 24, 36 or 60 mo after vaccination; no increased likelihood of ASD, regression, or parental concern after vaccination compared with before vaccination
DeWilde et al, <sup>19</sup> 2001	Case-control study: Compared changes in number of consultations 6 mo before to 6 mo after MMR vaccine administered in autistic patients and control subjects	No significant difference in change in number of consultations between autistic patients (0.69 consultations per patient decrease) and controls (0.73 consultations per patient decrease) ( $P = .69$ ); only 1 case of ASD diagnosed within 6 mo of MMR vaccination
Fombonne and Chakrabarti, <sup>20</sup> 2001	Cross-sectional study: Compared ages of first parental concern between population samples exposed to MMR vaccine and a pre-MMR vaccine sample Compared mean interval from MMR to parental concern in autistic children with and without regression	Mean ages of first parental concern in post-MMR vaccine samples were 19.3 and 19.2 mo; in pre-MMR samples, 19.5 mo ( $P > .05$ ) Mean interval in patients with ASD who had regression, 248 d; in patients with ASD who did not have regression, 272 d ( $P > .05$ )
Taylor et al, <sup>21</sup> 2001	Case series: Determined whether vaccine received before development of parental concern, after development of concern, or not at all in autistic children with GI tract symptoms or developmental regression	GI tract symptoms: 19% received MMR vaccine before parental concern, 15% after concern, and 16% did not receive MMR vaccine ( $P = .48$ ) Regression: 26% received MMR vaccine before parental concern, 26% after concern, and 30% did not receive vaccine ( $P = .83$ )
Madsen et al, <sup>22</sup> 2002	Retrospective cohort: Determined if an association existed between development of ASD and age at MMR vaccination or interval since MMR vaccination	No association between development of ASD and age at MMR vaccination ( $P = .23$ ) or interval since MMR vaccination ( $P = .42$ )
Makela et al, <sup>23</sup> 2002	Retrospective cohort: Determined if there was clustering of hospitalizations for autism after time of MMR vaccination	Of 535544 MMR vaccines, there were 309 hospitalized for autism after MMR vaccination; no clustering of hospitalizations detected in interval from MMR vaccination to hospitalization

Abbreviation: GI, gastrointestinal.

vaccination programs are introduced. Any comparison between MMR vaccinated and not vaccinated populations after the introduction of a vaccination program would also be confounded by the systematic differences that would exist between these 2 populations. We identified only 1 study that conducted a (retrospective) cohort analysis of rates of autism and ASD in children who received the MMR vaccine and those who did not.<sup>22</sup> This study, the highest validity evidence available on the existence of an association, found no difference in the rates of autism or ASD in these 2 populations. This study had sufficient power and was adjusted for some potential confounding variables.

The remaining studies we examined had to make use of alternative methods to address the hypotheses. Ecological designs such as time-series analyses were used to answer the question of whether changing rates in ASD were related to changing rates in MMR vaccination. These study designs are limited by the potential of erroneously drawing inferences on individuals from aggregate data. In addition, any observed association or lack of association could be confounded by secular trends in the

mechanism of diagnosis of ASD. However, despite these limitations the strength of evidence against an association observed in the studies we examined provides us with confidence that there is not an epidemic of ASD related to the MMR vaccine.

The more specific question of a link between the MMR vaccine and a rare variant form of ASD cannot be ruled out by such ecological analyses, however. This question also presents several methodological challenges and only 4 of the studies examined for this. The study by Pelto et al,<sup>14</sup> while providing useful information, had important limitations owing to the potential for reporting bias and the limited sample size of 31 children. The study by Makela et al<sup>23</sup> only examined for evidence of hospitalizations for inflammatory bowel disease in individuals hospitalized with autism after having received the MMR vaccine. This study would not have identified other forms of GI tract disease, or patients who were not hospitalized.<sup>23</sup> The study by Fombonne and Chakrabarti,<sup>20</sup> while directly examining for a link between variant autism and the MMR vaccine, was limited by the use of populations from 2 distinct periods and is susceptible to bias from

**Table 5. Specific Association of Variant Autism and Measles, Mumps, Rubella (MMR) Vaccine**

Source	Analysis	Results
Peltola et al, <sup>14</sup> 1998	Case series: Conducted follow-up of 31 vaccinated children reported to have GI tract symptoms (of about 3 million vaccine doses)	No cases of ASD in these children after mean follow-up of 9 y 3 mo
Fombonne and Chakrabarti, <sup>20</sup> 2001	Cross-sectional study: Compared rates of developmental regression in samples of autistic children before and after introduction of the MMR vaccine Compared mean interval from MMR to parental concern in autistic children with and without regression Determined rates of childhood disintegrative disorder after introduction of the MMR vaccine sample	Rate of any developmental regression reported in post-MMR sample = 15.6%; in pre-MMR sample = 18.4% ( $P > .15$ ) Mean interval in patients with ASD and regression, 248 d; in patients with ASD who did not have regression, 272 d ( $P > .05$ ) Low incidence of childhood disintegrative disorder in epidemiological sample after MMR vaccination (0.6/10 000)
Taylor et al, <sup>21</sup> 2002	Time series: Identified if there was an increasing percentage of children with ASD and either GI tract symptoms or regression between 1979 and 1998 (MMR vaccine introduced in 1998) Case series: Determined whether MMR vaccine received before development of parental concern, after development of concern, or not at all in autistic children with GI tract symptoms or developmental regression	No increase in percentages of children with ASD who had either bowel symptoms (OR, 0.98; 95% CI, 0.93-1.04; $P = .50$ ) or who had regression (OR, 0.98; 95% CI, 0.93-1.03; $P = .47$ ) over entire period GI tract symptoms: 19% received MMR vaccine before parental concern, 15% after concern, and 16% did not receive MMR vaccine ( $P = .48$ ) Regression: 26% received MMR vaccine before parental concern, 26% after concern, 30% did not receive MMR vaccine ( $P = .83$ )
Makela et al, <sup>23</sup> 2002	Retrospective cohort: Determined if any recipients of MMR vaccines hospitalized with autism were also hospitalized with inflammatory bowel disease	No hospital visits for inflammatory bowel disease among 309 children hospitalized with autism

Abbreviation: ASD, autistic spectrum disorder; CI, confidence interval; GI, gastrointestinal; OR, odds ratio.

secular changes in referral patterns or methods of diagnosis. The study by Taylor et al<sup>21</sup> was the highest-quality study examining this specific question and provides the strongest evidence against a link between variant autism and the MMR vaccine.

Perhaps the most convincing evidence that emerges from this review against a link between MMR and all cases of ASD is the data on temporal association. Eight studies examined this specific question using a variety of methods. The studies consistently demonstrated that children developed ASD at the same age, whether or not they were vaccinated and were not more likely to present after MMR vaccination. These results suggest that the initial temporal association between the MMR vaccine and ASD observed by Wakefield et al<sup>1</sup> was likely a chance association owing to the fact that the initial presentation of ASD is often around the time of the MMR vaccine.

The primary advantages of the review we have presented are the systematic methods we used for reducing bias in identifying and appraising literature and the presentation of data sorted by the type of hypothesis tested. We limited our review to epidemiological evidence and specifically chose not to include data from case reports or biological evidence. Although these other forms of evidence are useful in generating hypotheses, the epidemiological evidence we presented is the highest quality of evidence available to establish whether an association exists. However, the limitations of these data need to be recognized. For example, the study by Patja et al,<sup>13</sup> which relied on data from a passive reporting system for adverse events, identified no cases of autism in 1.8 million vaccinees. This is well below the normal incidence of the condition and suggests the presence of reporting bias. Several of the studies we included relied on records from services for children with disabilities for the diagnosis of ASD

and are susceptible to the misclassification of developmental disorders. Our review did not explore the link between the MMR vaccine and pathologic features of the GI tract that are not associated with ASDs. We also did not identify studies, or extract data in included studies, that only sought to determine if a variant form of autism existed and did not determine the association of this variant form of autism to the MMR vaccine.

The results of our review are consistent with the findings of other reviews. We particularly support the Institute of Medicine's findings that there is no evidence of an association between ASDs and the MMR vaccine although the ability of epidemiological studies to rule out an association between the vaccine and a rare form of ASD is limited.<sup>10</sup> Since the Institute of Medicine review was conducted, 2 further studies examining for the association between the MMR vaccine and a specific form of autism have been published and also showed no link.<sup>21,23</sup> Nevertheless, the overall quality of evidence against this particular association is not as high as the evidence against the other hypotheses.

## CONCLUSIONS

Our review finds no evidence of the emergence of an epidemic of ASD related to the MMR vaccine. It also finds no evidence of an association between a variant form of autism and the MMR vaccine although recognizing that relatively few studies have examined this specific question. The characterization of a variant form of autism remains the focus of considerable debate.<sup>24,25</sup> Given the current evidence, if a variant form of ASD exists that is associated with the MMR vaccine, it is sufficiently rare so as not to be identified by the current epidemiological studies.

### What This Study Adds

Given the results of a literature search for English and non-English language articles, there appears to be no evidence from epidemiological studies of (1) an increased rate of ASD in children who have received the MMR vaccine compared with those who have not, (2) an increase in ASD cases associated with the introduction of the MMR vaccine, (3) a temporal association of the MMR vaccine with ASDs. Four studies have examined the possibility of an association of the MMR vaccine and a new variant form of ASD and found no link, although some of these studies had important methodological limitations. However, if a variant form of ASD were associated with the MMR vaccine, it would have to be sufficiently rare so as not to be identified by these studies. If future studies are to be conducted, they should attempt to determine if an association exists between the MMR vaccine and specific phenotypes of ASD.

While the risk of autism from MMR remains theoretical, the consequences of not vaccinating are real with several studies demonstrating the health effect of reducing vaccination coverage.<sup>26,27</sup> Based on this evidence public health officials should continue to advocate vaccination with MMR while continuing to recognize public concerns. The potential association of ASD and the MMR vaccine occupies a particularly high-risk space among the general population by being both unknown and potentially catastrophic.<sup>28</sup> Risks of this type can cause substantial concern amongst the public that may appear irrational to public health officials. The public may require more studies ruling out an association between the risk factor and disease for these types of risks than other types. If future studies are conducted to examine this question, we recommend that they focus on identifying an association between the MMR vaccine and a specific phenotype of ASD rather than between the MMR vaccine and all forms of ASD.

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