



Measles, Mumps, and Rubella Vaccines and Diagnoses of Autism Spectrum Disorders among Children: A Meta-Analysis

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Abstract

Purpose: The authors of the study sought, through a meta-analysis of primary studies, to address the question “Are the odds of being diagnosed with an autism spectrum disorder (ASD) the same for those who receive a measles, mumps, and rubella (MMR) vaccination and those who do not?”

Background: Despite evidence from numerous sources failing to demonstrate consistent evidence of ASD diagnoses as a consequence of receiving MMR vaccinations, parents/guardians sometimes forego vaccinating their children.

Methods: Three researchers searched for and obtained relevant studies, and two researchers independently applied a standardized data extraction form to the included studies.

Results: Seven independent effect sizes were calculated, yielding a pooled random-effects $OR^* = 0.25$ (95% CI, LL = 0.09, UL = 0.76) (* denotes random-effects estimate). Under the fixed-effect model, the $OR = 0.33$ (95% CI, LL = 0.25, UL = 0.45).

Conclusions: The odds of ASD diagnoses attributable to receiving or not receiving an MMR vaccination are not indistinguishable within clinical limits of indifference. Even so, the odds of ASD diagnoses are substantially smaller for those receiving an MMR vaccination than for those who do not.

KEYWORDS: measles, mumps, and rubella vaccine, autism spectrum disorders, autism, meta-analysis

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Introduction

Autism spectrum disorders (ASDs) are complex neurodevelopmental conditions that impair interpersonal communication (e.g., verbal, non-verbal), social actions and interactions (e.g., sharing emotions, understanding how others think and feel, holding a conversation), and daily routines or behaviors (e.g., repeating words or actions, obsessively following routines or schedules, playing in repetitive ways) (National Institute of Child Health and Human Development 2001). Although widely considered idiopathic in origin, approximately one in 110 children—one in 80 boys and one in 240 girls—in the United States are diagnosed with an ASD (Centers for Disease Control and Prevention 2010; hereafter CDC). Males are nearly four times more likely to be diagnosed with ASDs than female children (CDC 2010). The probability of an ASD diagnosis decreases in children of Hispanic ethnicity and increases among those who have siblings with diagnoses of ASDs and chromosomal medical conditions such as Fragile X syndrome, tuberous sclerosis, and Down syndrome (CDC 2006; 2010).

In the late 1990s, controversies regarding the relationship between measles, mumps, and rubella (MMR) vaccines and diagnoses of ASDs began to arise when parents and guardians of children with an ASD, as well as autism action groups, began claiming that thimerosal, a preservative once contained in MMR vaccines, was causally associated with their children's autism (Baker 2008). Moreover, public opinion was further exacerbated by the Wakefield, Murch, and Anthony (1998) publication in *The Lancet* where it was concluded that MMR vaccines were causally associated with ASDs in children (Wakefield, Murch, and Anthony 1998). Since dissemination of that publication, some parents and guardians have shown reluctance to accept MMR vaccines for their children, in both the United States and the United Kingdom (Baker 2008). MMR vaccination rates have decreased in the United States and United Kingdom while the incidence of measles has increased (CDC 2008b).

In 2000, the Centers for Disease Control and Prevention (CDC) declared elimination of measles in the United States (CDC 2008b). Since that declaration, however, outbreaks of measles have occurred due to sporadic importations of measles, generally related to travel to other countries (CDC 2008b). In 2008, 131 (123 cases in United States residents) cases of measles were reported in the United States and 86 were reported in 2000, an almost two-fold increase since 2000 (CDC 2008a; 2008b). Of the 123 measles cases in United States residents, 112 occurred in persons unvaccinated or of unknown vaccination status (CDC 2008b). Children whose parents chose not to have them vaccinated comprised 91% of cases (CDC 2008b). Simultaneously, the number of measles cases in England and Wales increased to 1,001 cases in 2008, representing a 25-fold increase (Health Protection Agency 2011).

Given the incongruence in vaccination beliefs and the incidence rates of measles, numerous studies from 1998 to 2011 examined the association between MMR vaccines and ASD diagnoses. Most of the studies failed to show scientific evidence in support of parent, guardian, and autism advocacy groups' opinions (Aldridge-Sumner 2006; Fombonne et al. 2006; Fombonne and Chakrabarti 2001; Mrozek-Budzyn, Kieltyka, and Majewska 2010; Takahashi et al. 2003; Uchiyama, Kurosawa, and Inaba 2007). More importantly, in 2011, *The Lancet* recalled the Wakefield, Murch, and Anthony 1998 study because "It has become clear that several elements of the 1998 paper by Wakefield et al. are incorrect, contrary to the findings of an earlier investigation. In particular, the claims in the original paper that children were 'consecutively referred' and that investigations were 'approved' by the local ethics committee have been proven to be false. Therefore [*The Lancet*] fully retracted this paper from the published record" (The Editors of *The Lancet* 2010). Additionally, Godlee, Smith, and Marcovitch (2011) reported in the *BMJ* that only one of the 12 children in the Wakefield, Murch, and Anthony 1998 study actually developed regressive autism and that three children did not actually have a diagnosis of autism. Moreover, the General Medical Council 2010, which monitors physician activity in Britain, concluded that patients in the Wakefield, Murch, and Anthony 1998 study were selected conveniently, subjected to invasive medical procedures without regard to distress and pain, and that Wakefield, Murch, and Anthony 1998 conduct in the study was dishonest and irresponsible. Even so, and despite evidence from numerous reputable sources failing to demonstrate consistent evidence of ASDs due to MMR vaccinations, some parents and guardians continue to forego vaccinating their children against MMR due to fear that their children may develop an ASD (Baker 2008).

Two years after publication of the Wakefield, Murch, and Anthony 1998 study, reviews completed by the Institutes of Medicine (IOM), the American Academy of Pediatrics, and the United Kingdom Medical Research Council concluded that no statistical association existed between MMR vaccinations and incidence rates of ASDs (Charman 2002; Halsey, Hyman, and Conference Writing Panel 2001; Medical Research Council 2001; Stratton et al. 2001). Specifically, IOM conducted a review of all available evidence (completed studies, on-going studies, published medical and scientific papers, and expert testimonies) related to this supposed association and found no consistent link between MMR vaccinations and diagnoses of ASDs. Even so, the body of evidence repudiating the relationship between MMR vaccinations and ASD diagnoses has not thus far been sufficient to eliminate fears that MMR vaccines are causally associated with ASDs (Charman 2002).

Purpose

In the current investigation, the authors sought to statistically reinvestigate the relationship between MMR vaccinations and ASD diagnoses as reported in the Cochrane Collaboration's "Vaccines for Measles, Mumps and Rubella in Children" and in primary studies (Demicheli et al. 2005). From the Cochrane Collaboration research review, evidence of adverse events from MMR vaccines was reported, but the review's authors did not present statistical confirmation of the existence, or not of a reliable relationship between MMR vaccinations and ASD diagnoses. The central purpose of this study, therefore, was to systematically examine the statistical evidence between MMR vaccinations and diagnoses of ASDs. Specifically, the authors of the study sought, through a meta-analysis of primary studies, to address the question: "Are the odds of being diagnosed with an ASD the same for those who receive an MMR vaccination and those who do not?" The statistical hypothesis implied by this question is one of equivalence rather than superiority or non-inferiority (Blackwelder 1982). Under a hypothesis of equivalence, the odds of ASD diagnosis attributable to receiving or not receiving an MMR vaccination are deemed indistinguishable (i.e., equivalent) if the observed odds ratios (ORs) are within clinical limits of indifference. These limits were set to a conservative 20% symmetric equivalence range (i.e., between 0.80 and 1.20) based on standard medical industry practice as well as clinical significance (Blackwelder 1982). Stated in notational form, the null and alternative hypotheses of equivalence related to the focal research question were $H_0: OR \leq \delta_1$ or $OR \geq \delta_2$ and $H_A: \delta_1 < OR < \delta_2$, respectively, where $\delta_1=0.80$ and $\delta_2=1.20$.

Methods

Data Sources

Primary studies were searched for in the Cochrane Central Register of Controlled Trials (CENTRAL), Biological and Agricultural Index (1983–March 2011), Education Resources Information Center (ERIC) (1966–February, 2011), Dissertations and Theses (1860–March, 2011), Google Scholar, MEDLINE (1965–March, 2011), ProQuest (1971–March, 2011), PsycINFO (1887–March, 2011), PubMed (1949–March, 2011), Science Direct, Scopus (1995–March, 2011), and Web of Science (Science Citation Index Expanded (1900–March, 2011) and Social Sciences Citation Index (1956–March, 2011) using search terms for measles, mumps, and rubella vaccines (MMR, MMR vaccine, MMR

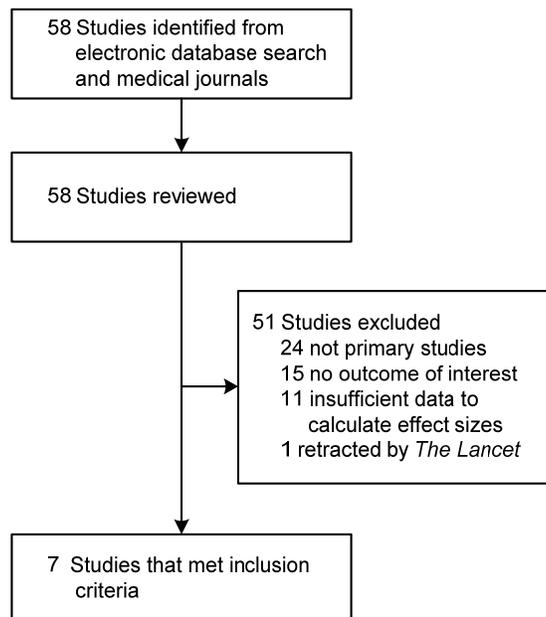
vaccination), autism spectrum disorders (autism, ASD). Additional primary studies were searched for by the reviewing reference lists of retrieved studies and also through searches in *BMJ*, *Journal of American Medical Association*, and *The Lancet*.

Study Selection

Studies were selected for analysis if they met the following inclusion criteria: (1) studies of the relationship between MMR vaccines and ASD diagnosis; (2) studies including reports of the number of cases with ASD, number of cases without ASD, number of cases who received MMR vaccine, and number of cases who did not receive MMR vaccines; (3) studies published in English language; and (4) studies with sufficient and appropriate data to directly extract or reliably calculate effect sizes in the form of ORs.

Initial searches identified 58 studies (Figure 1). Screening of titles and abstracts was completed by two of the authors (K.A.H., P.F.M.). Full reports of the 58 potentially relevant studies were independently evaluated by the two authors. From these studies, the two authors independently applied the inclusion criteria to determine inclusion or exclusion of studies for analysis. In all, seven studies met inclusion criteria.

Figure 1. Study Selection Process



Data Extraction

A piloted, standardized data extraction form was used to code information from the included studies (Wilson 2009). Through this process bibliographic information, features of study design, characteristics of the study population, and effect sizes were extracted and recorded. When necessary, ORs were calculated with p_T being the probability of an ASD diagnosis for a patient treated by an MMR vaccine (treatment) and p_C for a patient not receiving an MMR vaccination (control). For patients receiving an MMR vaccination, the odds that a patient would be diagnosed with an ASD was defined as

$$O_T = \frac{p_T}{1-p_T},$$

with the odds for control patients defined as

$$O_C = \frac{p_C}{1-p_C},$$

and where the OR between the treatment and the control was defined as

$$OR = \frac{O_T}{O_C} = \frac{\frac{p_T}{1-p_T}}{\frac{p_C}{1-p_C}}$$

The data extraction process was completed by two of the authors (K.A.H., P.F.M.). Reliability of the data extraction procedure for the proportion of observed agreement across all coding categories was, on average, $k_o=0.90$ and accounting for chance agreement was, on average, $k=0.80$ (Davey, Gugiu, and Coryn 2010). Disagreements arising from the data extraction process were resolved through a consensus-seeking procedure—the two authors who coded the studies deliberated the disagreements and arrived at mutually agreed upon data to extract. Table 1 shows the primary characteristics of the included studies (Aldridge-Sumner 2006; D’Souza, Fombonne, and Ward 2006; Fombonne et al. 2006; Fombonne and Chakrabarti 2001; Mrozek-Budzyn, Kieltyka, and Majewska 2010; Takahashi et al. 2003; Uchiyama, Kurosawa, and Inaba 2007).

Table 1. Primary Study Characteristics

Study	Publication Year	Research Design	Birth Year of Patients	Country	Geographic Region	Sample Size	OR
Fombonne and Chakrabarti	2001	Case-series	1992–1995	United Kingdom	Europe	194	0.02
Takahashi et al.	2003	Case-control	1988–1992	Japan	Asia	63	0.12
Aldridge-Sumner	2006	Cross-sectional	1971–Unknown	United States	North America	114	0.51
D’Souza, Fombonne, and Ward	2006	Case-control	Unknown	Canada	North America	88	1.65
Fombonne et al.	2006	Case-series	1987–1998	Canada	North America	180	0.61
Uchiyama, Kurosawa, and Inaba	2007	Case-series	1976–1999	Japan	Asia	769	0.63
Mrozek-Budzyn, Kieltyka, and Majewska	2010	Case-control	Unknown	Poland	Europe	288	0.05

Data Synthesis

To evaluate the main effect of receiving or not receiving MMR vaccinations on diagnoses of ASDs, both random-effects and fixed-effect meta-analysis models were used. The focal analysis for computing a weighted mean effect size across studies was conducted using a random-effects model. Under the random-effects model, the weight assigned to each study for computing the summary effect across studies was the within-study variance for each study plus the between-study variance. The random-effects model was selected for the focal analysis given that factors potentially influencing effect sizes were not considered consistent across all studies. Conversely, a fixed-effect model, in which all factors that could influence effect sizes are considered constant across studies, was also estimated. In the fixed-effect model study weights were computed as the inverse of study variances and were used to quantify heterogeneity. For subgroup analyses, a mixed-effects model was applied using a random-effects model within subgroups and a fixed-effect model across subgroups (Borenstein et al. 2009).

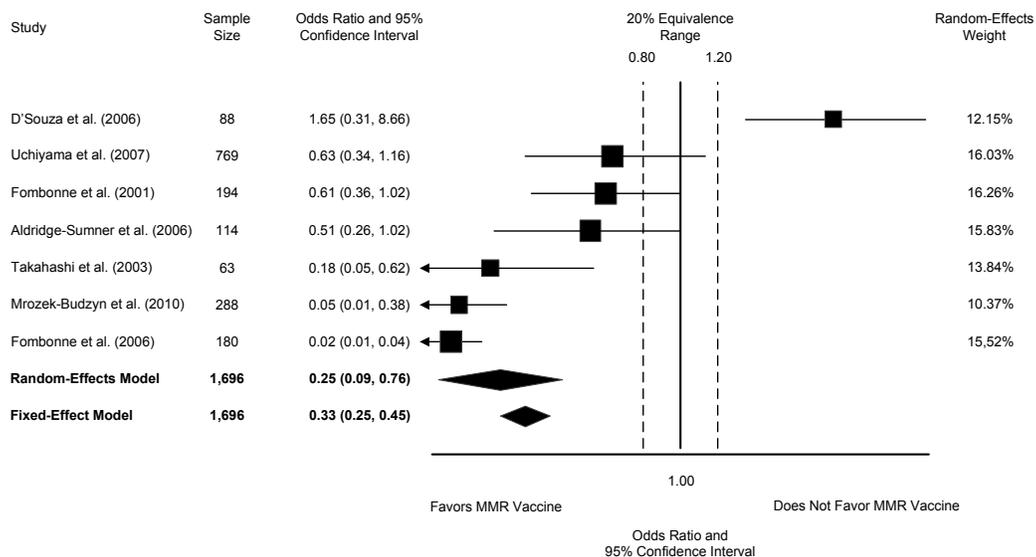
Secondary analysis, in the form of a mixed-effects meta-regression model, was also performed. Statistical analyses were conducted by three authors (C.L.S.C., P.F.M., K.A.H.). Throughout the planning, design, and execution of the meta-analysis the “Meta-Analysis of Observational Studies in Epidemiology (MOOSE)” checklist was followed (Stroup et al. 2000).

Results

Main-Effect Models

Under the random-effects model, the pooled main effect $OR^* = 0.25$ (*denotes random-effects estimate) with a 95% confidence interval (CI) having a lower limit (LL) of 0.09 and an upper limit (UL) of 0.76. Under the fixed-effect model, the summary main effect $OR = 0.33$ with a $LL = 0.25$ and an $UL = 0.45$. For the fixed-effect model $\tau^2 = 1.85$ and $\tau = 1.36$. The estimate of τ is interpreted as the standard deviation of the true effect, with τ^2 being the true effect variance. The forest plot in Figure 2 shows the sample sizes, OR^* s, 95% CIs, and random-effects weights for each independent-sample effect size as well as for the fixed-effect and random-effects models, including a 20% symmetric equivalence range ($OR \geq 0.80$ to $OR \leq 1.20$).

Figure 2. Forest Plot of Main Effect Meta-Analysis



Tests for Heterogeneity

Heterogeneity of effects was tested with the fixed-effect meta-analysis model using Q and I^2 statistics. The Q statistic (observed weighted sum of squares; WSS) and its corresponding p -value serve as a statistical test of the expected WSS and addresses the viability of the null hypothesis that the between-study dispersion is greater than would be expected only due to sampling error. Conversely, the I^2 statistic provides information regarding what proportion of observed variance is real and is a ratio with a range from 0% to 100%. An I^2 near zero indicates that between-study dispersion is attributable to random error and any attempt to explain the between-study variance is an attempt to explain something that is random. As I^2 increases, some of the between-study variance is real and potentially can be explained (Higgins et al. 2003). For the model, $Q(6)=68.39$ ($p<0.00$) and $I^2=91.23\%$. These results indicated that the observed between-study variability is greater than would be expected only due to sampling error and, therefore, that the observed effects of MMR vaccinations on diagnoses of ASDs likely vary over levels of one or more additional variables.

Tests for Publication Bias

To ascertain the likelihood or presence of publication bias a funnel plot of precision by OR in log units was produced (Sterne, Becker, and Egger 2005). In the absence of publication bias studies will be distributed symmetrically about the combined effect size in the plot. In the presence of bias the bottom of the plot would tend to show a higher concentration of studies on one side of the mean than the other. The magnitude of potential publication bias was statistically tested using Kendall's τ and Egger's Test of the Intercept (Sterne and Egger 2005). If asymmetry is caused by publication bias large standard errors will tend to be associated with larger effect sizes. These tests quantify bias captured by the funnel plot using the observed values of effect sizes and their precision. Tests for whether statistical adjustments were necessary in the presence of publication bias were examined using Duval and Tweedie's Trim-and-Fill method (Duval 2005). In the absence of bias the funnel plot would be symmetric about the summary effect. The Trim-and-Fill procedure imputes missing studies, adds them to the analysis, and then the summary effect size is recomputed. Rosenthal's Fail-Safe N test was applied to compute the number of missing studies that would need to be added to the analysis to yield a clinically insignificant overall effect (Becker 2005).

Visual inspection of the funnel plot revealed no observable indications of publication bias. Kendall's $\tau=-0.48$ with a one-tailed $p=0.07$ and a two-tailed $p=0.13$. Egger's Test of the Intercept produced an intercept of $\beta=-2.19$, with

$t(5)=0.65$, and a two-tailed p -value of 0.54. Duval and Tweedie's Trim-and-Fill procedure resulted in no imputed studies to the right or left of the mean. Rosenthal's Fail-Safe N indicated that 98 additional studies would need to be located and included in the analysis to produce an overall OR=1. Overall, no significant evidence of publication bias was identified.

Subgroup Analyses

In an effort to explain the heterogeneity observed in the focal analysis ($Q[6]=68.39$, $p<0.00$; $I^2=91.23\%$), subgroup analyses were performed using research design and country (collapsed to world geographical regions) as moderators (Table 1). Research design was selected as a potential moderator as case-series designs often are confounded by systematic selection biases as compared to case-control designs (Shadish, Cook, and Campbell 2002). Excluding the single study using a cross-sectional design (Table 1), heterogeneity was greater for case-series designs ($Q[2]=58.79$ [$p<0.00$]; $I^2=96.60\%$) than for case-control designs ($Q[2]=7.66$ [$p=0.02$]; $I^2=73.90\%$). Under the mixed-effects model, the case-series subgroup summary OR^{*}=0.20 (95% CI=0.03 to 1.43) and the case-control subgroup summary OR^{*}=0.25 (95% CI=0.04 to 1.63). Geographical region was selected as a potential moderator given variability in immunization coverage across countries as well as differential incidence rates of ASD diagnoses between countries (Clark and Sanderson 2009; Dyches et al. 2004; Williams 1990). By geographical region, heterogeneity was greater for North America ($Q[2]=46.02$ [$p<0.00$]; $I^2=95.65\%$) than for Europe ($Q[1]=5.36$ [$p=0.02$]; $I^2=81.34\%$) and Asia ($Q[1]=3.18$ [$p=0.07$]; $I^2=68.58\%$). Under the mixed-effects model, the North America summary OR^{*}=0.24 (95% CI=0.02 to 3.18), the Europe summary OR^{*}=0.21 (95% CI=0.02 to 2.48), and for Asia the summary OR^{*}=0.38 (95% CI=0.11 to 1.27). Neither the research design nor geographical region moderators fully explained the observed heterogeneity and differed only modestly from the heterogeneity explained by the main-effect meta-analysis.

Meta-Regression

To explore the relationship between MMR vaccinations and ASD diagnoses over time, a mixed-effects meta-regression estimated using the method of moments of publication year on log OR was conducted. Publication year was not a statistically significant predictor of log OR ($\beta=-0.17$, 95% CI=-0.66 to 0.32, $Z=-0.69$, $p=0.49$). The test that the publication year coefficient equaled zero was $Q_{model}^*=0.47$, $df=1$, $p=0.49$. Goodness of fit was evaluated against Q_{resid} (residual WSS using fixed-effect model weights) to estimate and test the variance,

τ^2 , of unexplained heterogeneity. For the model $Q_{resid}=4.57$, $df=5$, $p=0.47$, indicating that even with the publication year covariate in the model that some of the between-studies variance was unexplained.

Discussion and Conclusions

Due to the very nature of MMR vaccinations, randomized controlled trials (RCTs) of the effects of MMR vaccines on diagnoses of ASDs are ethically unfeasible (Cook et al. 2010). Even so, and although the odds of ASD attributable to receiving or not receiving an MMR vaccination are not statistically equivalent, the odds of ASD diagnoses are, however, substantially smaller for those receiving an MMR vaccination than for those who do not.

In the absence of a systematic quantitative synthesis, narrative methods (e.g., vote-counting, sign-tests) likely would conclude that the empirical evidence is inconclusive (Hedges 1980). This is particularly manifest in methods that emphasize p -values. Moreover, primary MMR studies related to ASD diagnoses, and included in the meta-analysis, exclusively applied tests of superiority rather than equivalence and, therefore, incorrectly specified focal hypotheses and statistical tests of those hypotheses (Blackwelder 1982).

Although the results of the meta-analysis are largely incongruent with the views and opinions of some groups, they do, nonetheless, provide reasonable empirical evidence supporting MMR vaccinations. Furthermore, results from subgroup analysis and meta-regression indicated that effects were not significantly moderated by methodological characteristics, geographical location, or over time and that those moderators did not explain differential effects (but does not exhaust the potential for other moderators) (Lipsey 2003). Nevertheless, since publication of the Wakefield, Murch, and Anthony 1998 study, MMR vaccination rates have decreased in the United States and United Kingdom while incidence rates of measles have increased (CDC 2008b).

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