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Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies

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ABSTRACT

There has been enormous debate regarding the possibility of a link between childhood vaccinations and the subsequent development of autism. This has in recent times become a major public health issue with vaccine preventable diseases increasing in the community due to the fear of a 'link' between vaccinations and autism. We performed a meta-analysis to summarise available evidence from case-control and cohort studies on this topic (MEDLINE, PubMed, EMBASE, Google Scholar up to April, 2014). Eligible studies assessed the relationship between vaccine administration and the subsequent development of autism or autism spectrum disorders (ASD). Two reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus with another author. Five cohort studies involving 1,256,407 children, and five case-control studies involving 9,920 children were included in this analysis. The cohort data revealed no relationship between vaccination and autism (OR: 0.99; 95% CI: 0.92 to 1.06) or ASD (OR: 0.91; 95% CI: 0.68 to 1.20), nor was there a relationship between autism and MMR (OR: 0.84; 95% CI: 0.70 to 1.01), or thimerosal (OR: 1.00; 95% CI: 0.77 to 1.31), or mercury (Hg) (OR: 1.00; 95% CI: 0.93 to 1.07). Similarly the case-control data found no evidence for increased risk of developing autism or ASD following MMR, Hg, or thimerosal exposure when grouped by condition (OR: 0.90, 95% CI: 0.83 to 0.98; $p = 0.02$) or grouped by exposure type (OR: 0.85, 95% CI: 0.76 to 0.95; $p = 0.01$). Findings of this meta-analysis suggest that vaccinations are not associated with the development of autism or autism spectrum disorder. Furthermore, the components of the vaccines (thimerosal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder.

1. Introduction

Over the past several years much concern has been raised regarding the potential links of childhood vaccinations with the development of autism and autism spectrum disorders (ASD). The vaccinations that have received the most attention are the measles, mumps, rubella (MMR) vaccine and thimerosal-containing vaccines such as the diphtheria, tetanus, pertussis (DPT or DT) vaccine. A rising awareness of autism incidence, prevalence, and the postulated causation of childhood vaccinations has led to both an increased distrust in the trade-off between vaccine benefit outweighing potential risks and an opportunity for disease resurgence. This is especially concerning given the fact that the CDC reported 17 measles outbreaks in the U.S. in 2011 and NSW, Australia also saw a spike in its measles notifications from late 2011 to mid-July 2012 [1,2]. Vaccine-preventable diseases clearly still hold a presence in modern day society and the decision to opt out of MMR or other childhood vaccination schedules because of concerns regarding the development of autism should be properly evaluated with available evidence. To date there have been no quantitative data analysis pooling cohort and case-control studies that have assessed the relationship between autism, autistic spectrum disorder and childhood vaccinations.

This meta-analysis aims to quantitatively assess the available data from studies undertaken in various countries regarding autism rates and childhood vaccination so that the relationship between these two, whatever its significance, can be adequately substantiated.

2. Methods

2.1. Study protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct our review and analysis [3,4]. The PRISMA guidelines have been

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developed in an attempt to standardise reporting in systematic reviews and include a four-phase flow diagram as well as a checklist of 27 items deemed necessary for transparent reporting of results of meta-analyses. A systematic search of the databases Medline (from 1950), PubMed (from 1946), Embase (from 1949), and Google Scholar (from 1990) through to April 2014, to identify relevant articles was completed. The following combinations or search terms were used to search all databases: vaccine; immunise; immunisation; autism; autistic; Asperger; pervasive developmental disorder and PDD. The search strategy was peer reviewed by two independent experts prior to implementation. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

2.2. Eligibility criteria

This review included retrospective and prospective cohort studies and case-control studies published in any language looking at the relationship between vaccination and disorders on the autistic spectrum. No limits were placed on publication date, publication status, or participant characteristics. Studies were included that looked at either MMR vaccination, cumulative mercury (Hg) or cumulative thimerosal dosage from vaccinations to ensure all proposed causes of ASD or regression were investigated. Outcome measures included development of any condition on the autistic spectrum as well as those specifically looking at regressive phenotype. Papers that recruited their cohort of participants solely from the Vaccine Adverse Event Reporting System (VAERS) in the United States were not included due to its many limitations and high risk of bias including unverified reports, underreporting, inconsistent data quality, absence of an unvaccinated control group and many reports being filed in connection with litigation [5,6]. We excluded studies that did not meet the inclusion criteria.

2.3. Study selection

Two authors (LT, AS) independently reviewed the abstracts and methods of returned results to assess for eligibility for inclusion. Disagreements between reviewers were resolved by consensus with the third author (GE).

2.4. Data collection process

Data was extracted manually by one author (LT) which was subsequently reviewed by another author (GE). Where data on multiple endpoints was available, the longest duration between exposure and measurement of outcome was used. Where data on multiple doses of mercury were available, the data used was that when the largest dose was given. Where data was provided adjusted for confounding variables, the result that was adjusted for the most variables was included. Duplicate publications were determined and excluded by juxtaposing authors' names, sample sizes of treatment and control groups, and subsequent odds and risk ratios.

2.5. Data items

Information was extracted from each paper on (1) study design; (2) country of study; (3) sample sizes (including total number of participants, and number of participants in each treatment arm); (4) intervention (including type, dose and timing of vaccination); (5) outcome measure (including development of autistic disorder, other autism spectrum disorder, or autistic disorder with regression); (6) and measures of effect (including calculated odds and risk ratios and the confounding variables for which they were adjusted).

2.6. Risk of bias in individual studies

Risk of bias was assessed independently by two authors (LT, AS) using the appropriate Newcastle-Ottawa scale (NOS) [7] with disagreements resolved by consensus with the other author (GE). The NOS scale has three components assessing studies on participant selection, comparability, and outcome/exposure assessment. A study is awarded stars for items within each category for a maximum of nine stars. We decided to rate studies as low risk of bias if they received nine stars, moderate risk of bias if they received seven or eight stars, and high risk of bias if they received less.

2.7. Statistical analysis

Pooled odds ratios and 95% confidence intervals were calculated for the effect of vaccinations on the development of autism using a random effects model [8]. For both case-control and cohort studies, an overall pooled odds ratio was calculated. Subsequently we divided the data and performed subgroup analyses to investigate risk of developing either autism alone or ASD alone after MMR, Hg, or thimersal exposure. In addition we performed subgroup analyses by exposure type investigating the individual likelihood of developing autism or ASD depending on whether the participants

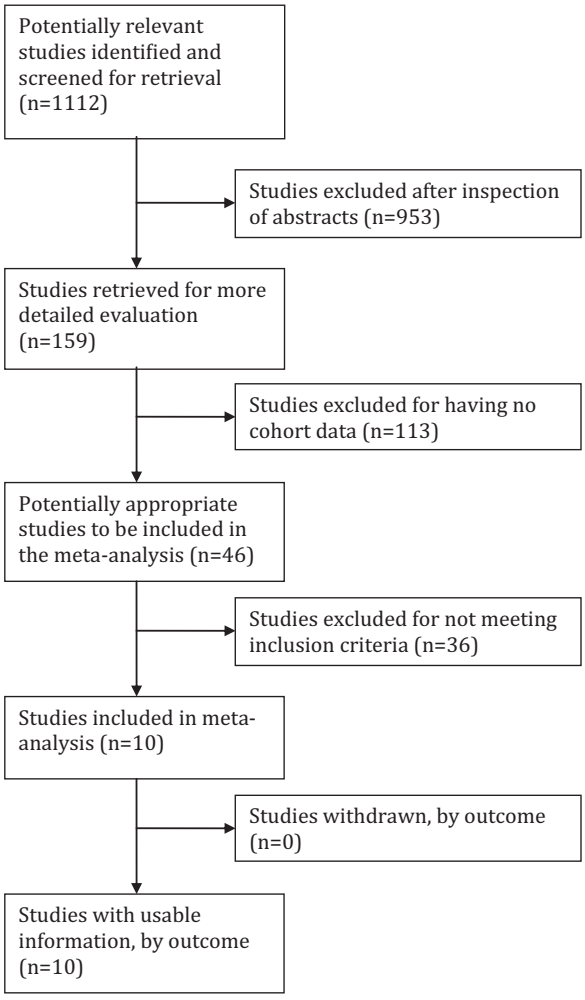

Fig. 1. Flowchart of search strategy.