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# *Thimerosal Exposure from Pediatric Vaccines and the Risk of Autism Spectrum Disorder: A Systematic Review of Multi-National Evidence*

**Mu Jiang**

*University College Maastricht, Maastricht University, Maastricht, The Netherlands*
*m.jiang@student.maastrichtuniversity.nl*

***Abstract.*** In response to increasing concerns about environmental factors linked to Autism Spectrum Disorder (ASD), thimerosal, an ethylmercury-based vaccine stabilizer, has received considerable attention. This paper evaluates multinational observational evidence on whether thimerosal exposure from pediatric vaccines is associated with ASD risk. Accordingly, six eligible studies from the USA, UK, Denmark, and Japan were selected in accordance with PRISMA 2020 guidelines, and study characteristics, exposure definitions, ASD diagnostic criteria, and effect estimates were extracted. Because study design and exposure measurement varied substantially, reported odds ratios, risk ratios, and hazard ratios were transformed to the natural-log scale and pooled using a generic inverse-variance random-effects model. In addition, risk of bias was assessed using the Newcastle-Ottawa Scale and visualized with robvis. The results showed a log effect of 0.19, with a 95% confidence interval of -0.49 to 0.88, corresponding to a pooled ratio of 1.21 with a 95% confidence interval of 0.61 to 2.41 and P=0.502, indicating no statistically significant association. However, heterogeneity was high, with I2=89.72% and P<0.001, mainly driven by two low-precision studies that suggested an increased risk. Notably, reduction of heterogeneity after removal of outliers did not change the overall finding of no significant or causal association between thimerosal exposure from pediatric vaccines and increased ASD risk.

***Keywords:*** Autism spectrum disorder, Thimerosal exposure, Pediatric vaccines, Vaccine safety, Meta-analysis

## 1. Introduction

With the increase in reported cases of Autism Spectrum Disorder (ASD), public concern has grown over potential environmental factors, like thimerosal, an ethylmercury-containing preservative used in some vaccines since the 1930s [1, 2]. Given that the subjects of children's vaccinations are healthy, any potential risks of neurodevelopmental disorders must be supported by large-scale, well-controlled epidemiological studies. Consistently, several population-based studies have reported no association between thimerosal-containing vaccines and ASD. In particular, cohort studies carried out in the United Kingdom and Denmark have yielded results near the null, while a case-control

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study in Japan found no increased ASD risk following early exposure to thimerosal-containing vaccines [3-5]. But two studies based on the Vaccine Safety Datalink reported elevated risk estimates, in contrast to the findings of the other studies [6, 7]. Furthermore, a large-scale meta-analysis of vaccine exposure and autism has failed to find a higher risk from mercury or thimerosal exposure [8]. This inconsistency may be attributed to differences in study design, exposure measurement, case ascertainment, study period, and confounding control, rather than a true causal relationship. Therefore, a focused synthesis on thimerosal may help clarify the direction and strength of the existing evidence. Based on previous studies, the extent of the association between thimerosal exposure from pediatric vaccines and ASD risk remains to be further evaluated. This review synthesizes multinational cohort and case-control studies, converts effect measures to the log scale for standardization, evaluates risk of bias, and conducts a pooled analysis to assess whether current observational evidence supports a statistically significant association.

## 2. Methodology

### 2.1. Systematic review and meta-analysis

Using keywords such as thimerosal, thiomersal, ethyl mercury, vaccine, vaccination, autism spectrum disorder, autism, and neurodevelopmental disorder, PubMed was systematically searched. Additional eligible studies were identified through manual screening of reference lists from relevant articles and reviews. This paper followed PRISMA 2020 guidelines for transparent study identification, screening, and eligibility assessment [9]. Peer-reviewed human observational studies published in English from 2000 onward were included if they evaluated pediatric exposure to thimerosal-containing vaccines or vaccine-derived mercury and reported ASD or related developmental outcomes. Non-English articles, pre-2000 publications, animal studies, non-peer-reviewed reports, and studies without ASD-related outcomes were excluded.

For each included study, extracted variables comprised study design, country, source population, sample size, age range, exposure definition and assessment, comparator group, ASD definition and diagnostic source, follow-up duration, effect measure, and statistical uncertainty. Accordingly, effect estimates reported as odds ratios, risk ratios, or hazard ratios were treated as comparable relative measures and log-transformed prior to synthesis; when standard errors were unavailable, they were derived from the 95% confidence interval using $\mathrm{SE}=[\ln(\text{upper CI})-\ln(\text{lower CI})]/3.92$. Given the low incidence of ASD, these measures were pooled as approximate relative risks after transformation. A generic inverse-variance random-effects model was applied due to expected heterogeneity in study design, setting, exposure definition, diagnostic approach, and follow-up structure [10]. Analyses were conducted in JASP, with data archived on the Open Science Framework. Risk of bias was assessed using the Newcastle-Ottawa Scale across selection, comparability, and exposure or outcome domains in non-randomized studies, with cohort and case-control designs evaluated separately for key bias domains. Beisdes, robvis was used to visualize bias judgments and summarize bias across studies [11, 12].

### 2.2. Prisma-guided study selection

The study selection process is shown in the PRISMA flow diagram in Figure 1. Initially, the PubMed search identified 202 records. Subsequently, screening excluded 12 non-English articles, 111 studies published before 2000, and 20 animal or non-relevant human studies, leaving 59 records for title and abstract screening. Of these, 17 studies were deemed eligible for full-text review, and 15

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full texts were obtained. During full-text assessment, studies were excluded if they did not report ASD-related outcomes, did not assess thimerosal or vaccine-derived mercury exposure, or were not peer-reviewed. In total, six studies met the inclusion criteria, including Andrews et al., Hviid et al., Uno et al., Young et al., Geier et al., and Price et al. [1, 3-7].

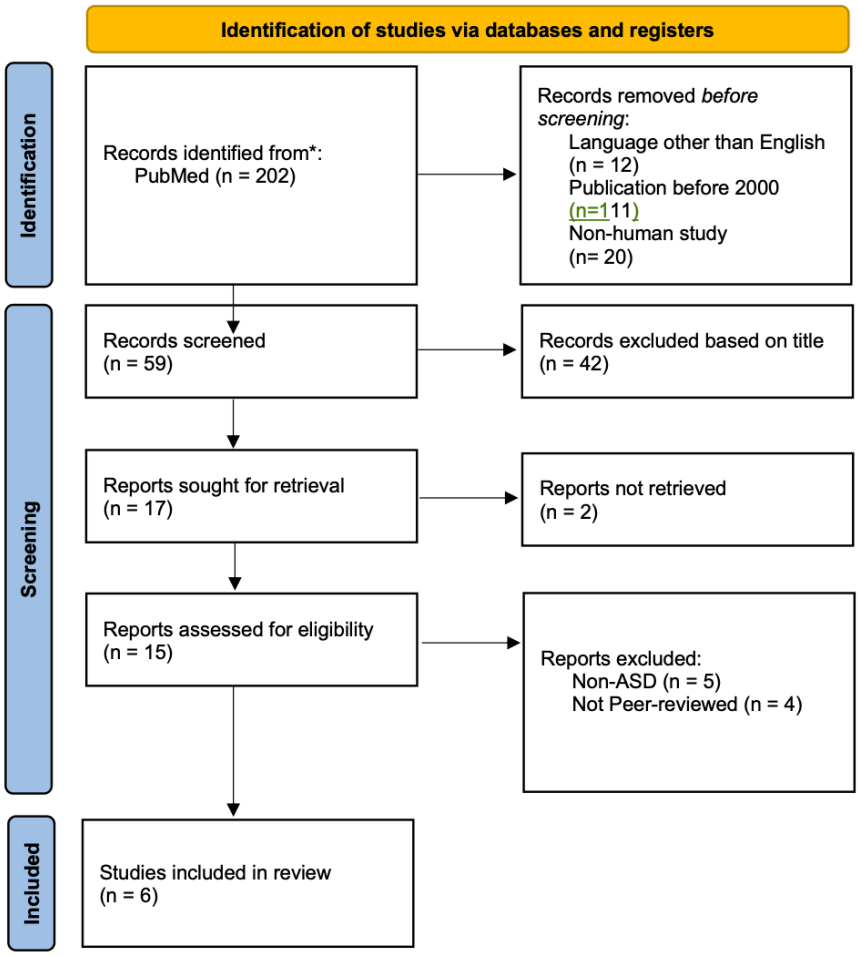


Figure 1. PRISMA flow of study selection

## 2.3. Characteristics of included studies and data items

The six included studies comprised three retrospective cohort studies and three case-control studies, conducted in Japan, the United States, Denmark, and the United Kingdom. Sample sizes ranged from a small clinic-based Japanese case-control study to large national or managed-care cohorts exceeding 100,000 participants. Besides, key study characteristics, like age range, exposure assessment, ASD diagnostic criteria, comparator group, and follow-up duration, were extracted due to their relevance to study comparability, as shown in Table 1. In terms of exposure assessment, methods differed across studies. Some relied on vaccination records to estimate cumulative mercury exposure, whereas others compared outcomes between thimerosal-containing and thimerosal-free vaccine exposure. Similarly, ASD ascertainment varied, such as registry-based ICD diagnoses, medical records, and standardized instruments like ADI-R, ADOS, DISCO, and DSM-based criteria.

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These methodological differences were considered key sources of heterogeneity and were taken into account in the interpretation of the meta-analysis, as shown in Table 2.

Table 1. Study characteristics

| Study | Country | Study design | Population | Non-cases | Cases | Age range |
|---|---|---|---|---|---|---|
| Uno, 2015 | Japan | Case-control | Yokohama Psycho-Developmental Clinic | 224 | 189 | 11–19 |
| Young, 2008 | USA | Retrospective cohort | Managed care organizations (MCOs) | 277,807 | 817 | 4–10 |
| Hviid, 2003 | Denmark | Retrospective cohort | National population registers | 466,223 | 1,227 | 1–11 |
| Price, 2010 | USA | Case-control | Managed care organizations (MCOs) | 752 | 256 | 6–13 |
| Andrews, 2004 | UK | Retrospective cohort | General Practice Research Database (GPRD) | 100,468 | 104 | 2–11 |
| Geier, 2013 | USA | Case-control | Vaccine Safety Datalink (VSD)/MCOs | 25,632 | 307 | Not specified (birth years 1991–1999) |

Table 2. Thimerosal exposure, comparators, outcomes, and follow-up

| Study | Exposure | Exposure assessment | Comparator | Outcome | Outcome assessment | Follow-up |
|---|---|---|---|---|---|---|
| Uno, 2015 | Early exposure to thimerosal-containing vaccines | Vaccination records | Age- and sex-matched non-ASD controls (1–2) | ASD | DISCO, DSM-5 | None |
| Young, 2008 | Thimerosal-containing vaccines | Vaccination records | Cumulative mercury dose | ASD (ICD-9 codes) | Diagnosis records | 4 years |
| Hviid, 2003 | Thimerosal-containing vaccines | Vaccination records | Thimerosal-free vaccines | ASD (ICD-10 F84.0–F84.9) | Psychiatric registry | Until diagnosis/death/emigration/age 11/2000 |
| Price, 2010 | Prenatal and infant exposure to thimerosal from vaccines/immunoglobulins | Vaccination records, maternal interviews | Matched non-ASD controls (age, sex, MCO) | ASD | ADI-R, ADOS | None |
| Andrews, 2004 | Thimerosal-containing vaccines | Vaccination records | Dose-level comparison | ASD (ICD-9 299.0) | Diagnostic codes | Mean 4.7 years (2–11) |
| Geier, 2013 | Thimerosal-containing hepatitis B vaccines | Vaccination records | No organic mercury exposure from hepatitis B vaccines | ASD | Diagnosis records | 7.29 years |

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## 3. Results

### 3.1. Risk of bias assessment

For all included studies, a formal risk-of-bias assessment was conducted, and the results are shown in Figure 2. Most studies were adequate in terms of the selection of exposed and comparison groups, especially the large registry-based and managed-care cohort studies. The main issues identified were confounding, exposure comparability, and outcome ascertainment. These are important concerns, as residual confounding may either overestimate or underestimate the effect size. For example, changes in the diagnostic criteria for ASD, calendar-period effects, healthcare utilisation, socioeconomic status, parental age, sex distribution, and access to specialist assessment may be associated with both recorded vaccination exposure and the likelihood of ASD diagnosis. Therefore, studies that do not adjust for these factors may show differences in estimated effects due to ascertainment or population structure rather than a true biological impact of thimerosal..

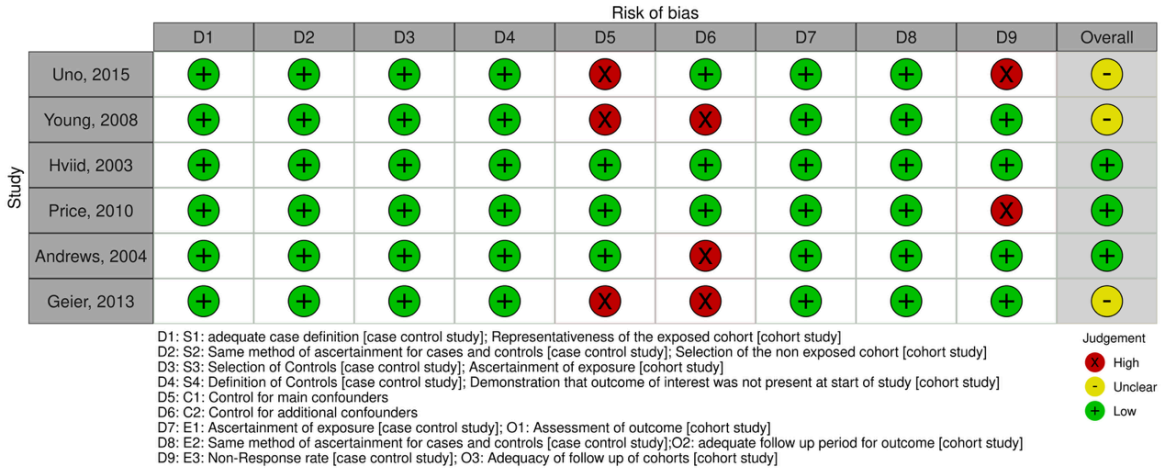


Figure 2. Risk of bias assessment

### 3.2. Effect estimates and meta-analysis

Table 3 shows the effect estimates obtained by the six main studies. To address mixed effect measures, ORs, RRs, and HRs were converted to log scale before pooling. Then, standard errors were derived from reported confidence intervals and used in a generic inverse-variance model. Afterward, pooled estimates were exponentiated to return to the ratio scale for interpretation. In general, study results were heterogeneous. Notably, Geier et al. and Young et al. reported statistically significant risk-increasing estimates, whereas Price et al. reported a statistically significant estimate below 1.0 [1, 6, 7]. Meanwhile, Uno et al., Hviid et al., and Andrews et al. exhibited confidence intervals crossing 1.0, indicating no statistical significance [3-5]. And these differences are probably due to methodological variations: the larger cohort studies used broad registry or database populations and had smaller standard errors, whereas the risk-increasing studies were less precise and more sensitive to exposure definition, diagnostic coding, and residual confounding. This indicates that a random-effects model and a cautious interpretation of the pooled estimate should be employed.

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Table 3. Data extraction from the primary studies

| Study | Effect measure | Main effect estimate | 95% CI lower | 95% CI upper | SE |
|---|---|---|---|---|---|
| Uno, 2015 | OR | 0.844 | 0.632 | 1.128 | 0.1478 |
| Young, 2008 | RR | 2.44 | 1.19 | 6.94 | 0.4503 |
| Hviid, 2003 | RR | 1.12 | 0.88 | 1.43 | 0.1239 |
| Price, 2010 | OR | 0.60 | 0.32 | 0.97 | 0.2829 |
| Andrews, 2004 | HR | 0.94 | 0.73 | 1.21 | 0.1292 |
| Geier, 2013 | OR | 3.39 | 1.60 | 7.18 | 0.3828 |

Note: CI = confidence interval; SE = standard error. All ratio measures were transformed to natural-log values before meta-analysis and back-transformed for interpretation.

### 3.3. Forest plot and sensitivity analysis

The random-effects meta-analysis of six studies showed high statistical heterogeneity ($I^2$ = 89.72%, $p < 0.001$), indicating substantial between-study variation, as shown in Figure 3. The pooled log effect was 0.19 (95% CI: -0.49, 0.88), corresponding to a pooled ratio of 1.21 (95% CI: 0.61-2.41; p=0.502). Because the confidence interval crossed 1.0, the pooled result did not provide statistically significant evidence of an association between thimerosal-containing pediatric vaccines and ASD risk. The random-effects model was appropriate because the studies differed in design, geographic setting, exposure metric, diagnostic method, and follow-up time. In addition, a sensitivity analysis excluding the two most visually influential risk-increasing outliers produced a pooled ratio close to the null (0.92; 95% CI: 0.76-1.12; p=0.418) and reduced heterogeneity to a moderate level ($I^2$ = 40.54%) [6, 7]. This suggests that the overall conclusion is not driven by a positive association, but by a few imprecise estimates.

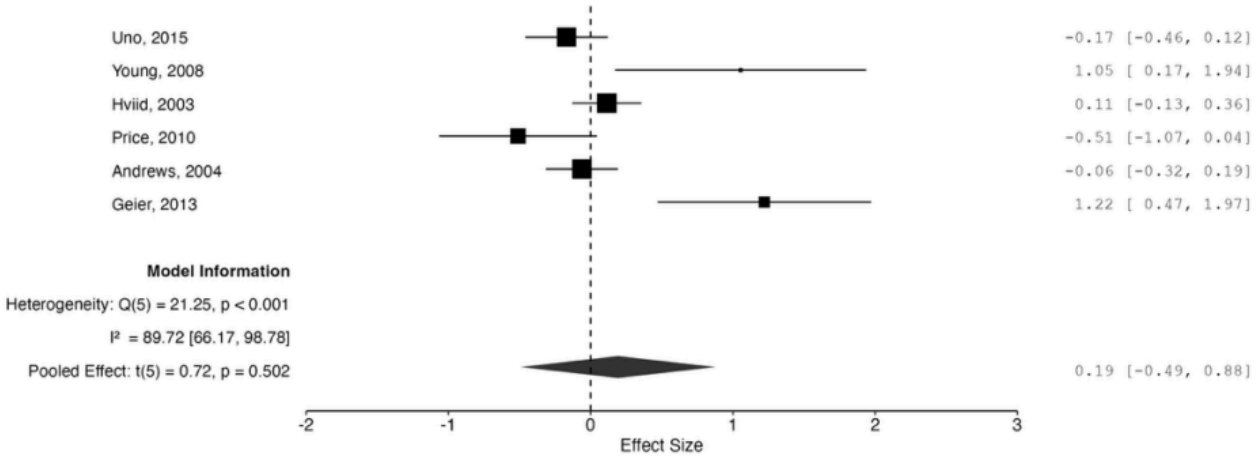


Figure 3. Forest plot and model information of all primary studies

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### 3.4. Funnel plot and publication bias

As shown in the funnel plot in Figure 4, there was visible asymmetry, and the two least precise studies were located on the right side of the pooled estimate [6, 7]. Egger's regression test was performed on the log-effect estimates and their standard errors to quantify the above pattern [13]. The intercept is positive but not statistically significant (intercept=2.10, p=0.319). This result does not offer formal statistical support for the small-study effect, and the power of the test is also very low given only six studies. Thus, the funnel plot is to be considered indicative rather than conclusive. If the small studies with null or protective results had not been published, the pooled estimate might have moved away from the null; alternatively, this asymmetry could stem from actual differences in the assessment of exposure and the identification of ASD.

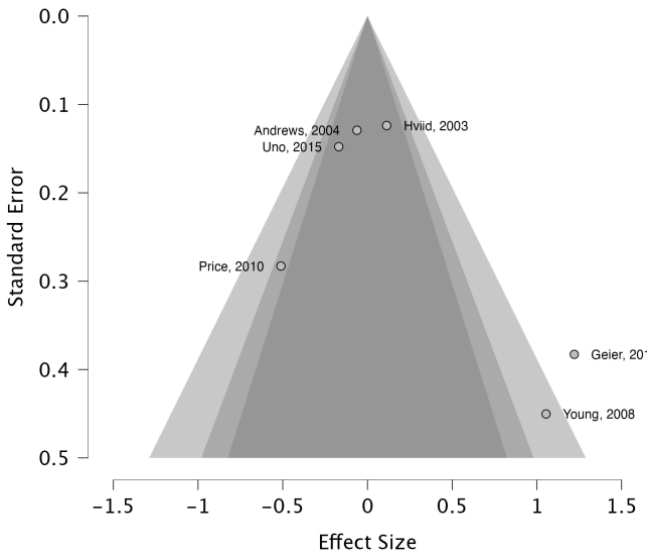


Figure 4. Funnel plot of all primary studies

## 4. Discussion

### 4.1. Interpretation of results

This study examined whether childhood exposure to thimerosal-containing vaccines is associated with increased ASD risk. Across six multinational observational studies, pooled results were not statistically significant, and overall evidence does not indicate increased risk. The source of the high heterogeneity is unclear. Large, precise cohort studies from Denmark and the UK showed estimates near the null, whereas the strongest risk-increasing results came from less precise VSD-based studies. Accordingly, sensitivity analysis excluding these outliers reduced heterogeneity and produced a pooled estimate close to 1.0. This pattern suggests that variation is more likely driven by differences in study design, exposure definition, and outcome ascertainment rather than a causal effect. In line with previous evidence, vaccine-autism studies have not found a link between mercury-containing vaccines or thimerosal and autism risk [8]. However, as all included studies are observational, the absence of a significant pooled association cannot be interpreted as definitive evidence of no effect. Overall, current epidemiological data do not support a statistically significant or causal association.

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### 4.2. Limitations of evidence

There are several limitations. Specifically, residual confounding remains possible, as factors such as parental age, sex, socioeconomic status, healthcare access, birth year, diagnostic delay, and changes in diagnostic criteria are associated with ASD and may not be fully balanced or adjusted between exposure groups. Besides, reliance on administrative diagnostic codes instead of standardized clinical assessments may lead to outcome misclassification. Moreover, exposure definitions were inconsistent across studies. Some estimated cumulative mercury exposure from vaccination records, while others used vaccine type comparisons or thimerosal-free groups, thus limiting comparability and precluding meaningful dose-response analysis. In addition, effect measures were heterogeneous. Although ORs, RRs, and HRs were transformed to a common log scale, this assumes approximate equivalence across measures, which remains an approximation even for rare outcomes. The small number of included studies limits assessment of publication bias. Egger's test was not significant, but with only six studies, small-study effects cannot be reliably excluded. Meanwhile, the search strategy was primarily based on PubMed and reference screening; although additional databases could yield further studies, most major international studies on this topic were already captured.

## 5. Conclusion

This study found no statistically significant association between thimerosal exposure from childhood vaccines and ASD. The pooled estimate was imprecise and heterogeneous, but excluding the two less precise risk-increasing studies in sensitivity analysis moved the estimate closer to the null and reduced heterogeneity. However, the main limitations included residual confounding, inconsistent exposure measurements, mixed effect measures, and a limited number of studies available for publication bias analysis. At present, multinational observational data do not support a causal link between thimerosal-containing infant vaccines and autism spectrum disorder. Therefore, public health communication should therefore differentiate between isolated positive findings and the overall weighted evidence base. Future research should standardize exposure and ASD definitions, clearly report confounding factors, and conduct prespecified sensitivity analyses across study subgroups.

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