Autism Occurrence by MMR Vaccine Status Among US Children With Older Siblings With and Without Autism FREE

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ABSTRACT

Importance Despite research showing no link between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorders (ASD), beliefs that the vaccine causes autism persist, leading to lower vaccination levels. Parents who already have a child with ASD may be especially wary of vaccinations.

Objective To report ASD occurrence by MMR vaccine status in a large sample of US children who have older siblings with and without ASD.

Design, Setting, and Participants A retrospective cohort study using an administrative claims database associated with a large commercial health plan. Participants included children continuously enrolled in the health plan from birth to at least 5 years of age during 2001-2012 who also had an older sibling continuously enrolled for at least 6 months between 1997 and 2012.

Exposures MMR vaccine receipt (0, 1, 2 doses) between birth and 5 years of age.

Main Outcomes and Measures ASD status defined as 2 claims with a diagnosis code in any position for autistic disorder or other specified pervasive developmental disorder (PDD) including Asperger syndrome, or unspecified PDD (International Classification of Diseases, Ninth Revision, Clinical Modification 299.0x, 299.8x, 299.9x).

Results Of 95 727 children with older siblings, 994 (1.04%) were diagnosed with ASD and 1929 (2.01%) had an older sibling with ASD. Of those with older siblings with ASD, 134 (6.9%) had ASD, vs 860 (0.9%) children with unaffected siblings ($P < .001$). MMR vaccination rates (≥1 dose) were 84% (n = 78 564) at age 2 years and 92% (n = 86 063) at age 5 years for children with unaffected older siblings, vs 73% (n = 1409) at age 2 years and 86% (n = 1660) at age 5 years for children with affected siblings. MMR vaccine receipt was not associated with an increased risk of ASD at any age. For children with older siblings with ASD, at age 2, the

adjusted relative risk (RR) of ASD for 1 dose of MMR vaccine vs no vaccine was 0.76 (95% CI, 0.49-1.18; P = .22), and at age 5, the RR of ASD for 2 doses compared with no vaccine was 0.56 (95% CI, 0.31-1.01; P = .052). For children whose older siblings did not have ASD, at age 2, the adjusted RR of ASD for 1 dose was 0.91 (95% CI, 0.67-1.20; P = .50) and at age 5, the RR of ASD for 2 doses was 1.12 (95% CI, 0.78-1.59; P = .55).

Conclusions and Relevance In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.

INTRODUCTION

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Two doses of measles-mumps-rubella (MMR) vaccine are currently recommended for children in the United States: the first at age 12 to 15 months and the second at age 4 to 6 years.1 Although a substantial body of research over the last 15 years has found no link between the MMR vaccine and autism spectrum disorders (ASD),2- 4 parents and others continue to associate the vaccine with ASD.5 Parents cite vaccinations, especially MMR, as a cause of ASD6 and have deferred or refused vaccinations for their children as a result.7,8 Lower vaccination levels threaten public health by reducing both individual and herd immunity and have been associated with several recent outbreaks of measles, with most cases occurring among unvaccinated individuals.9

Families with a child affected by ASD may be particularly concerned about reports linking MMR and ASD, despite the lack of evidence.10 Surveys of parents who have children with ASD suggest that many believe the MMR vaccine was a contributing cause.11 This belief, combined with knowing that younger siblings of children with ASD are already at higher genetic risk for ASD compared with the general population,12- 14 might prompt these parents to avoid vaccinating their younger children. In a recent survey of 486 parents of children with ASD, nearly 20% had declined or delayed MMR immunization in the younger siblings of these children.15 Furthermore, a Canadian study of 98 younger siblings of children with ASD found that younger siblings were less likely to be fully MMR immunized when compared with their older siblings with ASD. However, there were no statistically significant differences in rates of ASD diagnosis between immunized and nonimmunized children.10 To our knowledge, this very small study is alone in examining MMR immunization and ASD outcomes among the younger siblings of children with ASD.

Thus, we set out to report on ASD occurrence by MMR vaccine status in a large sample of US children having older siblings with ASD and to compare findings with those among children who have older siblings without ASD.

METHODS

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A retrospective cohort study was conducted using an administrative claims database associated with a large US health plan (the Optum Research Database). The Optum Research Database includes more than 34 million individuals each year, containing both commercially insured individuals and Medicare managed care enrollees. The database consists of proprietary, deidentified health claims data from a geographically diverse US population (16% West, 20% Midwest, 36% South, and 27% Northeast). In addition, the age and sex distribution of the enrollees is similar to that reported by the US Census Bureau for both the commercially insured and the Medicare managed care populations. The New England Institutional Review

Board waived the need for informed consent and deemed the study exempt based on its use of existing, deidentified16 data.

Index children were identified among commercially insured enrollees who had both medical and pharmacy coverage and included all children in the database born between January 1, 2001, and December 31, 2007, who were continuously enrolled in the health plan from birth to at least 5 years of age and who also had an older sibling continuously enrolled in the health plan for at least 6 months between the beginning and end of the study period (January 1, 1997-December 31, 2012). Older siblings of index children were identified using a family identifier variable associated with the insurance policy; siblings had to be between 6 months and 17 years older than the index child to be included.

ASD status in index children and older siblings was determined using a claims-based algorithm with a positive predictive value of 87%17 that required 2 or more claims on separate dates of service with an InternationalClassification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code in any position for autistic disorder, other specified pervasive developmental disorder (PDD) including Asperger syndrome, or unspecified PDD (299.0x, 299.8x, and 299.9x). Both index child and older sibling ASD status were determined using their entire enrollment time that fell within the study period. Index children had to have at least 1 older sibling with 2 claims with ASD diagnoses or all older siblings with no ASD diagnoses. Children with an older sibling with only 1 claim with an ASD diagnosis were excluded. Index children with only 1 claim with an ASD diagnosis were also excluded.

MMR vaccine receipt was defined as having a Current Procedural Terminology (CPT) or ICD-9-CM procedure code indicating receipt of each component (measles, mumps, and rubella) between birth and 5 years of age (eTable 1 in the Supplement). The date of administration of the trivalent MMR (or the last-administered component of monovalent vaccines) was used to determine age at administration for each dose (first or second).

Because the recommended age of first MMR dose administration is 12 to 15 months, and 4 to 6 years for the second dose, relative risks (RRs) were estimated to compare ASD status in children receiving 1 dose of MMR at ages 2, 3, 4, and 5 years and 2 doses at age 5 years vs those who were unvaccinated at those ages (2-dose RRs at age 4 years would only include those children who received the second dose by their fourth birthday). Separate RRs were estimated for children with older siblings with and without ASD. Since no children were lost to follow-up before reaching age 5, unadjusted RRs were reported as cumulative incidence rate ratios by taking the ratio of the proportion of children who had an ASD diagnosis in an exposed group (either 1 MMR dose or 2 MMR doses) to the proportion of children who had an ASD diagnosis in the unvaccinated group at a given age.

Adjusted RRs were reported as hazard rate ratios estimated from a single Cox proportional hazard regression model that used age since birth as the time scale and included MMR receipt as a time-varying covariate ascribing follow-up time to either the unvaccinated group, the 1-dose group, or the 2-dose group, depending on immunization status at any given age. An interaction term between MMR receipt and older sibling ASD status was included to allow adjusted RRs to vary by older sibling ASD status. In addition, interactions between MMR receipt and age (to relax the proportionality assumption and allow hazard ratios [HRs] to vary by age), as well as a 3-way interaction between MMR receipt, age, and older sibling ASD status, were tested for possible inclusion in the final model.

Both time-varying and fixed covariates were also included in adjusted models to control for potential confounding. Separate claims-based indicators of the presence of seizures and vaccine-related allergies in the index child were included as time-varying covariates because they are possible contraindications to vaccines and are potentially associated with ASD status.18- 20 To capture aspects of the index child's overall health status that might also be associated with both MMR receipt and ASD status, an indicator for preterm birth and a modified claims-based version21 of the childhood chronic conditions score (CCC)22

were included as fixed covariates. The modified CCC uses claims-based diagnosis codes to capture the presence of chronic conditions, excluding those associated with ASD, within 9 domains: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defects, and malignant neoplasms. The presence of at least 1 claim for a condition within each domain between birth and age 2 adds 1 point to the CCC score (range, 0-9). eTable 2 in the Supplement lists ICD-9-CM codes used to define conditions and variables.

Maternal and paternal educational level, household income, and race/ethnicity were also included as fixed covariates. These sociodemographic factors have been associated with both ASD status23 and vaccine receipt.24 Approximately 30% of the race/ethnicity data in this study were collected directly from public records (eg, driver's license records), while the remaining data were imputed using commercial software (E-Tech by Ethnic Technologies) that uses algorithms developed with US Census data zip codes (zip + 4) and first and last names. This imputation method has been validated and demonstrates 97% specificity, 48% sensitivity, and 71% positive predictive value for estimating the race of black individuals.25 Individuals categorized as other/unknown for race/ethnicity were those whose race/ethnicity could not be assigned by the imputation algorithm or who were added to the data set after the imputation had been performed.

Other fixed covariates included in the adjusted models were sex of the index child, mother's and father's age at index child's birth, geographic location defined by the 4 US Census regions, mental health benefits, and index child birth year, which was included to adjust for varying opportunity for ASD to develop or be diagnosed. Response categories were created for unknown or missing values of all covariates and included as such in regression models.

A series of sensitivity analyses were conducted to explore the influence of potential MMR or ASD status measurement error on results. Quantitative bias analyses were implemented for both exposure and outcome misclassification following the approach described by Lash et al.26 More detail on bias analysis methods is provided in the online supplement (eAppendix and eTable 3 in the Supplement). In addition, associations between MMR receipt and ASD risk were also reestimated using a less-restrictive 1-claim criterion for ASD diagnosis in younger siblings. An additional sensitivity analysis was also performed rerunning final models on the subset of children with no missing data on any covariates.

Statistical significance testing of unadjusted rate ratios was conducted using the Yates $\chi 2$ test, and statistical significance testing of hazard ratios estimated by maximum likelihood were conducted using Wald $\chi 2$ statistics. Likelihood ratio tests were used to test the statistical significance of Cox proportional hazards models with and without interaction terms. All statistical tests were 2-sided and the α level for all tests was .05. Analyses were performed using SAS statistical software, version 9.2.

RESULTS

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Out of 95 727 children in the cohort, 1929 (2.01%) had an older sibling with ASD. Overall, 994 (1.04%) children in the cohort had ASD diagnosed during follow-up. Among those who had an older sibling with ASD, 134 (6.9%) were diagnosed with ASD, compared with 860 (0.9%) diagnosed with ASD among those with siblings without ASD ($P < .001$). The MMR vaccination rate (≥1 dose) for the children with unaffected siblings (siblings without ASD) was 84% (n = 78 564) at 2 years and 92% (n = 86 063) at age 5 years. In contrast, the MMR vaccination rates for children with older siblings with ASD were lower (73% at age 2 years [n = 1409] and 86% [n = 1660] at age 5 years).

Table 1 shows the clinical and sociodemographic characteristics of the 95 727 children, stratified by older sibling ASD status. Birth years were roughly equally distributed over 2001-2007, and slightly more than half

of the sample was male. Approximately three-quarters of participants were white, 3% were black (vs 13% in the US population), and 9% were Hispanic (vs 17% in the US population).27 All 4 of the major geographic regions in the United States were represented, with somewhat more representation in the South (42% vs 38%) and less in the West (17% vs 24%) as compared with the overall US population.27 Approximately 3% had a potential contraindication to vaccine receipt and approximately 8% were preterm. The average length of continuous enrollment was slightly more than 7 years.

Table Graphic Jump Location Table 1. Characteristics of Study Sample Stratified by Older Sibling ASD Status

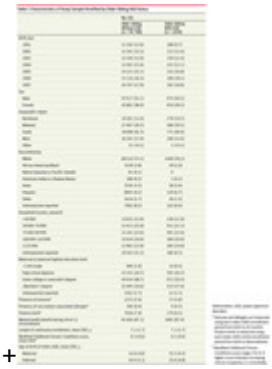

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Table 2 includes unadjusted RRs of ASD (cumulative incidence rate ratios) associated with receiving either 1 or 2 MMR doses (vs no doses) at ages 2, 3, 4, and 5 years separately in children with and without older siblings who had ASD. The unadjusted RR of ASD for 1 dose of MMR at age 2 years among children with unaffected older siblings was 0.80 (95% CI, 0.44-1.47; P = .58) and 0.44 (95% CI, 0.15-1.29; P = .22) among children with older siblings with ASD. Similarly, at ages 3, 4, and 5 years, no association was found between 1 dose of MMR and ASD among index children, irrespective of whether their older siblings had ASD. For 2 doses of MMR at age 5 years, the unadjusted RR of ASD was 0.74 (95% CI, 0.55-0.99; P = .049) among children with unaffected older siblings and 0.44 (95% CI, 0.26-0.75; P < .01) among children with older siblings with ASD.

Table Graphic Jump Location Table 2. Unadjusted and Adjusted Relative Risk Estimates for MMR Vaccination and ASD at Ages 2 to 5 Years in Children With Older Siblings With and Without Diagnosed ASD

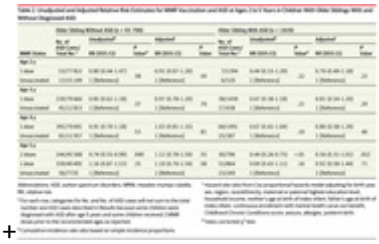

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Table 2 also shows adjusted RRs (hazard rate ratios) of ASD estimated from the Cox proportional hazards model. Interactions between MMR receipt and older sibling ASD status, as well as MMR receipt and younger sibling age both significantly improved the fit of a main effects–only model (P = .048 and P = .015, respectively) and were thus retained in the final model. The addition of the 3-way interaction between MMR receipt, age, and older sibling ASD status provided no additional improvement in model fit (P = .38) and was not retained.

In general, adjusted 1-dose RR estimates were closer to the null than unadjusted estimates and none of the 1-dose RR estimates at any age were statistically significant. At age 2 years, the adjusted RR of ASD for

those receiving 1 dose of MMR compared with those not receiving vaccine was 0.91 (95% CI, 0.67-1.20; P = .50) among children with unaffected siblings and 0.76 (95% CI, 0.49-1.18; P = .22) among children whose older siblings had ASD. At age 5 years, the adjusted RR of ASD for the same comparisons of 1 MMR dose vs no vaccine was 1.10 (95% CI, 0.76-1.54; P = .58) and 0.92 (95% CI, 0.58-1.44; P = .71). There appeared to be a similar influence of adjustment on the 2-dose RR estimates at age 5 years. The adjusted 2-dose RR estimate in children with affected older siblings was 0.56 (95% CI, 0.31-1.01; P = .052) while in children with unaffected older siblings the adjusted 2-dose RR was 1.12 (95% CI, 0.78-1.59; P = .55).

Quantitative bias analysis suggested that the influence of potential underreporting of MMR immunization in our claims data on RR estimates would be modest and toward the null. More detail is provided in eTable 3 (Supplement). Nondifferential outcome misclassification, if present, would appear to have a very small additional biasing effect toward the null. Differential outcome misclassification, if present, would most likely manifest as greater outcome detection sensitivity among children who were vaccinated vs those who were not, and would make actual RRs smaller than those reported (eTable 3 in the Supplement). These bias analyses are informative but need to be cautiously interpreted given the assumptions involved.

In other sensitivity analyses, we saw that results were not substantively different in Cox models that used the presence of just 1 claim with ASD to define the outcome (eTable 4 in the Supplement). In addition, the original Cox model was rerun excluding the 19% of the sample that was missing some sociodemographic data; again, results were not substantially changed (eTable 5 in the Supplement).

DISCUSSION

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Consistent with studies in other populations,2- 4 we observed no association between MMR vaccination and increased ASD risk among privately insured children. We also found no evidence that receipt of either 1 or 2 doses of MMR vaccination was associated with an increased risk of ASD among children who had older siblings with ASD. As the prevalence of diagnosed ASD increases, so does the number of children who have siblings diagnosed with ASD, a group of children who are particularly important as they were undervaccinated in our observations as well as in previous reports.10,15

Although there were no statistically significant RR estimates indicating increased ASD risk at any age in either group of children (those whose older siblings had or did not have ASD), the statistically significant interactions in the final Cox model suggest differences in RR by both age and older sibling ASD status. The pattern in RRs across these groups was such that lower RR estimates (commonly extending into the protective range, ie, below 1.0) were observed at younger vs older ages and in children with older siblings with vs without ASD. Although protective estimates tended not to reach statistical significance, this pattern is worth further consideration. It is possible, for example, that this pattern is driven by selective parental decision making around MMR immunization, ie, parents who notice social or communication delays in their children decide to forestall vaccination. Because as a group children with recognized delays are likely to be at higher risk of ASD, such selectivity could result in a tendency for some higher-risk children to be unexposed. To be consistent with observed data, this would need to happen more often at younger ages. This seems feasible because by the time the child is older, developmental concerns are more likely to have been confirmed or ruled out and parents may then be less worried about a new exposure, such as a vaccination, influencing a child’s developmental trajectory. Estimates at older ages would thus be less susceptible to bias related to selective parental decision making, which also aligns with the pattern observed here. This explanation would also suggest that the estimate for the 1-dose RR estimate at age 5 years (1.10; 95% CI, 0.76-1.54) is least vulnerable to this bias because age 5 is several years removed from the time parents are typically deciding about the first MMR dose or weighing the importance of early developmental concerns.

We also saw this tendency toward lower RR estimates for children whose older siblings had ASD, vs those with unaffected older siblings. As seen in our data and other studies,10,15 MMR immunization is lower in children with older siblings with ASD. It is also plausible that parents of affected older siblings would be especially attentive to developmental delays in their younger children and decide to forestall immunization. Developmental abnormalities in affected older siblings may also have appeared and raised parental concerns prior to encounters generating ASD claims. Also the contrast in the estimates for the adjusted RRs between children with and without older ASD-affected siblings was highest for those who received 2 doses at age 5; the ratio of the adjusted RR estimates at this age being 2.0 (1.12:0.56) for 2 doses compared with 1.19 (1.10:0.92) for 1 dose. This could reflect more older siblings having been diagnosed with ASD between the younger siblings' recommended ages of first- and second-dose administration, potentially leading parents to raise de novo concerns about the vaccine's safety at the time second dose decisions are being made.

This study used a large administrative claims data set spanning a recent 11-year period to examine associations between MMR immunization status and ASD risk in the United States. The administrative claims database allowed for the estimation of associations free from potential recall bias. However, administrative claims data do present some important research limitations. Because claims are generated for payment, diagnoses and procedures that do not affect payment are likely underreported, diagnoses for conditions that may eventually be ruled out can be overreported, and procedures and services that individuals receive through other payers may not be captured. For example, the MMR immunization rates in our study were 4% to 14% lower than rates reported in the National Immunization Survey. Thus, children in our study who are considered unvaccinated may have received vaccines in settings such as schools or public health clinics in which claims were not submitted. Additionally, the diagnosis of ASD was determined using a claims-based algorithm with a positive predictive value of 87%. There may have been children with ASD, for example, who did not receive care related to their ASD during the study period. However, we conducted a series of quantitative bias analyses to assess the potential effect of these measurement errors and do not believe these strongly influence the findings of this study. There are also potential inaccuracies in the identification of siblings from claims because of assumptions made about family relationships among individuals on the same health plan. However these are unlikely to be systematically related to either immunization status or ASD diagnosis.

For children born after a hypothetical link between MMR and autism risk was introduced, parental suspicion of developmental delay could influence MMR immunization decision making. Although the extent of this phenomenon is unknown, its existence is one explanation for the pattern of some of the RRs observed here. However, at ages and doses for which this phenomenon would be least likely to operate, there is no evidence of an association between MMR and autism risk.

These data and results are based on privately insured children with an extensive period (5 years) of continuous enrollment in a single health plan and may not be completely generalizable to other groups. The prevalence of ASD among all index children in the study sample was 1.04%, comparable with the current estimate of ASD prevalence of 1.5% in the general US population.28 In addition, the younger siblings of children with ASD had a 6.9% risk of ASD, also consistent with published estimates ranging from 6.4% to 24.7%.12- 14 Despite the large sample size for the entire study, the RR estimates for the children with older siblings with ASD are based on a modest number of children (1929 children including 134 with ASD). Yet, the upper bound of the CI never exceeded 1.44, implying that any true large effects are unlikely to be masked because of statistical imprecision. The findings of this study may not be as applicable to more ethnically and socioeconomically diverse populations that have less access to health care services. For example, in our population, the average age of ASD recognition based on claims was 4 years, several months earlier than the average age of ASD diagnosis in the US population of 4 years 5 months.28

CONCLUSIONS

In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of ASD, regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD.

ARTICLE INFORMATION

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Author Contributions: Ms Buikema and Dr Bancroft had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jain, Marshall, Buikema, Newschaffer.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Jain, Marshall, Buikema, Newschaffer.

Critical revision of the manuscript for important intellectual content: Jain, Marshall, Buikema, Bancroft, Kelly, Newschaffer.

Statistical analysis: Jain, Buikema, Bancroft, Newschaffer.

Obtained funding: Jain, Marshall, Newschaffer.

Administrative, technical, or material support: Marshall, Bancroft, Kelly.

Study supervision: Jain, Marshall, Buikema.

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