DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Mental Health
6001 Executive Boulevard
Bethesda, Maryland 20892

September 19, 2019

Allison Lucas, Esq.
Siri & Glimstad LLP, NY, NY
200 Park Avenue
Seventeenth Floor
New York, NY 10155

Re: FOI Case No. 52826

Dear Ms. Lucas:

This is our final response to your September 13, 2019 Freedom of Information Act (FOIA) request addressed to Mr. Garcia-Malene, NIH FOIA. You requested a copy of the Lewin Group for Study of Health Outcomes in Children with Autism and Their Families referenced by the NIH Special Notice found on the https:www.fbo.gov website.

Enclosed are 134 pages responsive to your request. This report was previously posted online.

Please contact me on 301-443-6130 or at LALBERTS@NIH.GOV if you have questions about your request. If you are not satisfied with the processing and handling of this request, you may contact the NIMH FOIA Public Liaison:

6001 Executive Blvd, Suite 6200
Bethesda, MD, 20892-9667
301-443-4335 (phone)
NIMHFOIA@mail.nih.gov (email)

In certain circumstances provisions of the FOIA and Department of Health and Human Services FOIA Regulations allow us to recover part of the cost of responding to your request. Because the cost is below the $25 minimum, there is no charge for the enclosed materials.

Sincerely,

Lisa D. Alberts
FOIA Coordinator
National Institute of Mental Health

Enclosure: 134 pages

Report 2: Vaccinations and Related Health Outcomes

Final Report

Prepared for:

NIMH

Submitted by:

The Lewin Group, Inc.

March 31, 2014

Executive Summary

Introduction and Study Objectives

This study is an extension of a larger project sponsored by the National Institute of Mental Health (NIMH), entitled the "Study of Health Outcomes in Children with Autism and Their Families." The current research, "Study of Vaccinations & Health and Neuropsychiatric Outcomes in Younger Siblings of Children with Autism Spectrum Disorders (ASD)," uses data from Optum's research database containing medical claims from the large health plan affiliated with Optum.

The overall purpose of this study is to further understand the extent of vaccination and under-vaccination with recommended childhood vaccines (including *Haemophilus influenzae* type b [Hib], rotavirus vaccine [RV], pneumococcal conjugate vaccine [PCV] and measles, mumps, rubella [MMR]) among younger siblings in families with older siblings some of whom have and others who do not have ASD. We also examined the rates of common vaccine-related infectious disease outcomes in both vaccinated and unvaccinated children. A final objective was to examine the association between the younger siblings' MMR vaccination status and the development of ASD or other neuropsychiatric health outcomes among children with an older sibling with ASD and children with an older sibling without ASD.

The specific objectives of this study and report were the following:

- Describe how select vaccine-related infectious disease outcomes (including otitis media, pneumonia, meningitis, and gastroenteritis) are related to vaccination receipt, including any potential associations with ASD status.
- Describe how ASD and neuropsychiatric health outcomes are related to MMR vaccination receipt, including any potential associations with older sibling ASD status.

Study Design and Analytic Strategy

This retrospective claims data study used medical data, pharmacy data, and enrollment information from the "Optum research database" (ORD) containing claims from the large health plan affiliated with Optum. Claims data for the period 01 January 1997 to 31 December 2012 were linked to a consumer database for select sociodemographic information including race, household income and education level. All study subjects were identified among commercial enrollees who have both medical (including behavioral) and pharmacy coverage. In addition to the overall (A1*) sample, specific subgroups were identified for the analyses in this report. These subgroups, C1-36* and C1-60* included children with continuous enrollment from birth to 36 months of age, and from birth to 60 months of age, respectively.

The medical chart validation study we completed in the initial portion of this project demonstrated that requiring at least 2 claims for ASD (the category we refer to as "likely ASD") generated a positive predictive value approaching 90%. In the previous reports we therefore restricted our sample to the "likely ASD" cohort. Similarly, in this study we limit the definition of having an older sibling with ASD to instances where the older sibling met criteria for "likely ASD." We also decided to eliminate altogether the 1,032 otherwise eligible index children whose identified older siblings met only criteria for "possible ASD" from the analyses presented in this report – since including them in the group of children without ASD may also have introduced misclassification.

As the research questions in this report each used different analytical approaches, they have been separated by research question below.

Vaccine-related Infectious Disease Outcomes

The multivariable analyses used stratified Cox models to address the research questions regarding vaccination-related infectious disease outcomes which examined the associations between vaccination status and the associated infectious disease (i.e., MMR vaccination and measles, mumps or rubella; RV vaccination and gastroenteritis; Hib and PCV vaccination and otitis media, pneumonia and/or meningitis). These models allow the shape of the baseline hazard function to vary across different event episodes accommodating, for example, the fact that the risk of an event can be lower (or higher) for a given second occurrence, compared to that for a first occurrence, at a given age. All regressions were estimated in the C1-36* population, that is, among index children meeting the sample selection criteria and who were continuously enrolled from birth through *at least* 36 months of age. Index children had a minimum of 36 months of continuous enrollment, but were followed from birth to the end of their enrollment period (>60 months on average) to capture vaccination exposures and outcomes of interest. We limited the gastroenteritis model to observations for index children born during or after 2006 because RV was not FDA approved until 2006.

We estimated unadjusted models for each set of vaccinations and associated infectious disease outcomes, as well as fully adjusted models that accounted for multiple covariates. For each model, additional covariates were finalized based on clinical rationale, descriptive analysis results, and statistical significance. In addition to vaccination status, the potential of index child ASD status to confound the relationship between index child vaccination status and the risk of vaccine-related infectious disease outcomes was considered and incorporated into this analysis. To explore this relationship, we estimated separate specifications of each fully adjusted model that included an indicator for possible/likely ASD vs. no ASD.

ASD and Other Neuropsychiatric Health Outcomes

The multivariable analyses used Cox proportional hazard regression models to examine the associations between MMR vaccination status, older sibling ASD status, and index child ASD status (likely/possible or no ASD). In these models, index child ASD diagnosis was the outcome, and MMR vaccination was a three-level (0, 1, or 2 doses), time-varying covariate. All regressions were estimated among index children meeting the inclusion criteria who were continuously enrolled from birth through at least 60 months of age (C1-60* subgroup; n = 96,054). Separate models were constructed defining the outcome as likely ASD and also as likely or possible ASD.

Each index child was observed for ASD outcome for a variable period of *at least* 60 months, from birth through the end of follow-up. Cox proportional hazards models allow the risk of detecting ASD to change at different ages (essentially adjusting for age) but assume that the ratio of the hazards across different MMR vaccine exposure groups are constant at different ages (i.e., across time). Because this assumption of proportionality of hazards is restrictive, we estimated all of the models with interaction terms between age (i.e., time) and MMR vaccination status which relaxes the proportionality assumption. These interaction terms allowed us to explore whether the hazard ratios comparing risk of ASD across different levels of MMR vaccination (0, 1 or 2 doses) changed at different ages.

We also wanted to explore the possibility that older sibling ASD status confounded or modified the relationship between index child MMR vaccination status and the risk of ASD. To do this we included an interaction term between MMR vaccination status and older sibling ASD status in addition to the interaction between age and MMR vaccination status. This results in the generation of separate age-specific MMR hazard ratios for index children with and without older siblings with ASD.

Results

Our results include the following: the association between vaccination and the infectious disease outcomes of interest (MMR, gastroenteritis, otitis media, pneumonia, and meningitis); and the association between MMR vaccination status and ASD status.

- Rotavirus vaccine appears protective against gastroenteritis as vaccination is associated with a **7.1% decrease in the risk of an initial gastroenteritis infection**. No statistically significant association between vaccination and gastroenteritis was found for **subsequent infections**.
    - A child's ASD status did not confound the relationship between rotavirus vaccination status and gastroenteritis infections, however **ASD was associated** with an increased risk of gastroenteritis infections (HR=1.27; 95% CI=1.11-1.45).
- In our results Hib and PCV vaccines appeared to be associated with an **increased risk** of otitis media and pneumonia episodes.
    - Children with a complete Hib vaccination series were **32% more likely** to have an otitis media infection and **16% more likely** to have pneumonia compared to being unvaccinated.
    - Similarly, children with a complete PPV vaccination series were **23% more likely** to have an otitis media infection and **13% more likely** to have pneumonia relative to being unvaccinated.
- Neither Hib nor PCV vaccination status were significantly associated with the occurrence of meningitis, but meningitis was rare in our sample (721 infections), resulting in non-significant hazard ratios with wide confidence intervals.
- MMR vaccination **was not** significantly associated with MMR infections (HR=0.99; 95% CI= 0.80-1.24). This was likely related in part to the rarity of these outcomes in the sample (408 total cases) and the resulting statistical imprecision.
- The risk of recurrence—defined as the risk of ASD in families in which there is already an older sibling with (Likely) ASD—was **7.5%** for Likely/Possible ASD and **5.8%** for Likely ASD.
- There was **no statistically significant association between MMR vaccination - either one or two doses—and ASD** at any age, irrespective of the one or two claim criteria for diagnosing ASD.
    - Furthermore, neither one nor two doses of MMR vaccine was associated with a statistically significant increase in ASD risk among children with an older sibling with ASD or among children with an older sibling who did not have ASD.

Conclusions

In summary, rotavirus vaccination appeared protective against gastroenteritis but we did not find evidence supporting immunizations as protective against other infectious disease outcomes (MMR infections, meningitis, otitis media, and pneumonia). The lack of association between MMR vaccination status and risk of ASD that we observed is consistent with and confirms the existing body of evidence on MMR immunization and ASD risk. Our study adds to the literature by providing the first evidence suggesting that MMR vaccination is NOT associated with ASD among a group of children at increased risk for ASD by virtue of having an older sibling with ASD. This novel finding may help to alleviate any lingering concerns among parents and professionals that the overall safety of the MMR vaccines may not extend to particular subgroups of children.

Our study resulted in the following conclusions and implications:

- The detected increased risk of gastroenteritis of 7.1% associated with a lack of rotavirus vaccination may appear modest but is clinically significant, especially when considering that the definition of the gastroenteritis outcome in these claims data is broad and undoubtedly includes many non-rotavirus gastroenteritis cases in addition to rotavirus cases.
- The potential increased risk of otitis media and pneumonia episodes associated with receiving Hib and PCV vaccines may be due to both lack of outcome specificity and the presence of surveillance bias.
- The inability to detect an association between vaccinations and the rare outcomes of MMR and meningitis was hampered by the small number of MMR infections in the data set (408 for MMR and 721 for meningitis) as well as the by the protection afforded by high levels of herd immunity.
- Some of the children in our study who appear unvaccinated may have received vaccinations in settings that were not included in their claims data; such misclassification would also bias our results against showing a protective effect of vaccinations.
- The association between MMR and ASD was not significant and remained insignificant among children who are at increased risk of ASD by virtue of having an older sibling with ASD.
- While surveillance bias likely impacted many of our results, such a bias would distort our results *towards* revealing a positive association between vaccination and ASD as both are associated with greater use of health services. Thus, our finding of no association, despite surveillance bias, strengthens, rather than weakens, our results that confirm the lack of risk of ASD from the MMR vaccination.

This study, in its ability to use a large and recent dataset that is reflective of the US population to construct large cohorts of children with older siblings, both with and without ASD, is both larger and more up-to-date than many comparable studies of children with ASD. The data spans an 11 year period, and the definition of ASD was validated using a chart study.[1] By examining the association between MMR vaccine and ASD in a group of children who were at increased risk of ASD (by virtue of having an older sibling with ASD), we begin to discredit the notion that there may be special subgroups of children who are susceptible to vaccination-related

neurodevelopmental adverse effects. And while a claims database cannot measure parental beliefs or reasoning for vaccination decisions, it does measure actual behaviors instead of relying on retrospective associations or parental reports of vaccination practices or ASD diagnoses.

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I. Introduction

A. Continuation of Study

This study is an extension of a larger project sponsored by the National Institute of Mental Health (NIMH), entitled the "Study of Health Outcomes in Children with Autism and Their Families." The current research, "Study of Vaccinations & Health and Neuropsychiatric Outcomes in Younger Siblings of Children with Autism Spectrum Disorders (ASD)," uses data from Optum's research database containing medical claims from the large health plan affiliated with Optum.

The overall purpose of this study is to further understand the extent of vaccination/under-vaccination with recommended childhood vaccines (including *Haemophilus influenzae* type b [Hib], rotavirus vaccine [RV], pneumococcal conjugate vaccine [PCV] and measles, mumps, rubella [MMR]) among younger siblings in families with older siblings with and without ASD. We also examined the rates of common vaccine-related infectious disease outcomes in both vaccinated and unvaccinated children. A final objective was to examine the association between younger sibling MMR vaccination status and ASD or other neuropsychiatric health outcomes in both the children with an older sibling with ASD and children with an older sibling without ASD.

The new research is organized into two reports, the first of which (Report 1) was submitted to NIMH in its final form on November 25, 2013. Reports 1 and 2 have the following aims:

1) **Report 1 – Sample Identification and Vaccination Rates of Younger Siblings:**
    - Identify a birth cohort of children from 2001-2011 with an older sibling including children with an older sibling with ASD (2+ diagnoses) and children whose older siblings have no evidence of ASD. Determine if the vaccination rates measured in the administrative claims database are comparable to the rates measured in the National Immunization Survey (NIS).
    - Examine vaccination patterns within families to determine if there is an association between ASD among older siblings and vaccination practices among younger siblings.
    - Examine vaccination patterns within families to determine if there is an association between the most proximal older siblings' MMR vaccination status and vaccination practices among younger siblings.
2) **Report 2 –Vaccine-related Infectious Diseases and ASD and Neuropsychiatric Health Outcomes among Younger Siblings:**
    - Describe how select vaccine-related infectious disease outcomes (including otitis media, pneumonia, meningitis, and gastroenteritis) are related to vaccination receipt, including any potential associations with ASD status.
    - Describe how ASD and neuropsychiatric health outcomes are related to MMR vaccination receipt, including any potential associations with older sibling ASD status.

The focus of this report is to present the background, methods, and results related to the two aims listed under Report 2 above.

B. Background

Both the popular press and the medical literature confirm that parents are concerned about a possible link between childhood vaccines and the development of autism.[2,3] Despite the lack of scientific evidence for this assertion, and an official retraction of the study that made the original claim, parents continue to cite a potential association as a reason to defer or refuse vaccinations, MMR in particular.[4] Accordingly, our previous analyses as presented in Report 1 found that both an older child's ASD status and an older sibling's lack of MMR vaccination were associated with lower rates of MMR vaccination in younger siblings, and also lower vaccination rates for Hib, PCV, and rotavirus vaccine. One explanation for the association between having an older sibling with ASD and not receiving the MMR vaccination could be that having a child with ASD increases parental worries about the risk of ASD related to the safety of vaccinations compared to parental levels of concern before their older child's ASD diagnosis. But the consequences of missing vaccinations, in families both with and without a child with ASD, are unknown. Therefore, one objective of this study is to determine if there is an association between vaccination status and contracting a vaccine-related infectious disease among younger siblings of children with and without ASD.

While the lack of empirical support for any association between MMR and ASD risk is impressively consistent,[5,6,7,8,9,10,11,12,13] no study completed to date has had the ability to focus on the subgroup of children who already have an older sibling with an ASD. These children are at increased risk for ASD, with recent published estimates of ASD sibling recurrence risk ranging between 6.1% and 18.7%.[14,15] Presumably, this increased risk is largely a function of shared genetic susceptibility factors among older and younger siblings.[14,15] A persistent criticism of the body of evidence that has emerged refuting an association between MMR and ASD risk is that the effect might be restricted to a genetically susceptible subgroup.[16] Consequently, exploring possible associations in siblings of older children with an ASD could generate some insight on the plausibility of this criticism. Thus, the second component of this study uses our large sample of younger siblings with enrollment from birth until five years of age to examine any association between MMR vaccination and ASD taking into account older sibling ASD status. To guard against the event that the ASD cases are too few in number to allow definitive conclusions, we also explore the relationship between MMR vaccination and a broad set of neuropsychiatric conditions that might include early markers of ASD.

II. Study Objectives and Research Questions

The overall purpose of Report 2 is to describe the relationship between vaccination receipt and health outcomes in children, specifically vaccine-related infectious diseases and ASD. This study first examined vaccine-related infectious diseases and whether having a diagnosis of ASD confounded the relationship between receiving vaccinations and infectious diseases. Next, we studied whether MMR vaccine receipt was associated with having ASD and whether having an older sibling with ASD modified this relationship. We list the specific research questions below.

A. Vaccine-related Infectious Diseases and Vaccination Receipt

1. What is the association between Hib, RV, PCV and MMR vaccination receipt and vaccine-related infectious diseases – including measles, mumps and rubella infections, otitis media, pneumonia, meningitis, and gastroenteritis?
2. Does having a diagnosis of ASD confound the relationship between Hib, RV, PCV and MMR vaccination receipt and vaccine-related infectious diseases – including measles, mumps and rubella infections, otitis media, pneumonia, meningitis, and gastroenteritis?

B. ASD and Other Neuropsychiatric Health Outcomes

1. What is the recurrence rate of ASD—i.e., among the index children who have an older sibling with ASD, what is the rate of ASD among the younger siblings?
2. What is the association between MMR vaccination receipt and ASD as well as a broad set of neuropsychiatric health outcomes?
3. Does having an older sibling with ASD modify the relationship between MMR vaccination receipt and ASD status?

The remainder of this report describes the data and methods used in addressing these research questions and the results, conclusions, and implications of our analyses. Section III describes the overall study design, including data sources, eligibility criteria, sample identification, and variable definitions. Section IV and V are organized by the two groups of research questions: vaccine-related infectious disease outcomes and ASD and other neuropsychiatric health outcomes. Each of these sections includes background on the topic, the causal diagram, analytic approach, results, and discussion. Finally, Section VI concludes the report with a summary of key findings and a discussion of implications. Additional information is included in the Appendices, which are referenced throughout the report.

III. Study Design

This retrospective claims data study used medical claims data and enrollment information from the "Optum Research Database" (ORD), the administrative claims database from the large health plan affiliated with Optum. Claims data for the period 01 January 1997 to 31 December 2012 were linked to a consumer database for select sociodemographic information. All study subjects were identified among commercial enrollees who had medical and pharmacy coverage. Seven main samples of index children were identified for this study, including the portion of the study documented in Report 1. The samples were identified based on varying continuous enrollment criteria and older sibling continuous enrollment criteria as described below in Section III.C.

This section outlines the details of our study design, including a) an overview of the database that was the source for study sample selection and the claims data-based analyses; b) the reviews that were required for study approval; c) a description of the sample design, including subject eligibility criteria, analytical subgroups and observation periods; and d) descriptions of select analytical variables constructed for the study analyses.[i]

A. Data Sources

1. Claims Data Source

Optum has access to a proprietary research database which contains medical (including mental health) and pharmacy claims data with linked enrollment information covering the period from 1993 through 2012. For 2012, data relating to approximately 12.6 million individuals with both medical and pharmacy benefit coverage are available. The underlying population is geographically diverse across the US and reasonably representative of the privately insured US population.

- **Medical Claims**
  - Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room, outpatient office, surgery center, etc.) for all types of covered services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers (e.g. physicians) use the HCFA-1500 or CMS-1500 format.[17] Claims for facility services submitted by institutions (e.g., hospitals) use the UB-82, or UB-92, or UB-04 format.[18,19] Medical claims include: diagnosis codes recorded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM); procedures and services recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Approximately six months following the delivery of services is required for complete medical data due to lags in claims

[i] Portions of the methodology and results that informed this study were drawn from the original contract Task A: Baseline Claims Analyses and Task A: Chart Study reports. Details are included in the companion reports that were submitted to NIMH on October 17, 2011 and March 2, 2012, respectively

submissions, adjudication, and final claims processing. In this report, the term "medical claims" is used to refer to claims for both physical and mental health care that were submitted and processed for reimbursement. Health care services not processed as a medical claim (e.g. care provided as part of a wellness program or as an Employee Assistance Program) are not included.

2. Sociodemographic Data

Many aspects of health care utilization and cost, including treatment selection, therapy patterns, and the diagnoses of health conditions, may depend on factors not directly measured in administrative claims data. For example, a vast literature has demonstrated differences in a variety of health conditions and services among patients of differing educational attainment, income, net worth, race/ethnicity, and family composition.[20, 21] To allow for more powerful insight into the prevalence and burden of illness, Optum has linked a unique source of patient-level data to the ORD that allows for analysis of some sociodemographic characteristics. The sociodemographic data are derived through a match done by the health plan with a marketing database maintained for a large segment of the US population. The available data elements include race, ethnicity, homeowner status, occupation type (e.g., blue collar, white collar, self-employed), education level, household income category, and household net worth category. The data populating these sociodemographic elements are generated by a combination of self-report, modeling, census data, and a variety of other individual-level and population-level data sources.

The sociodemographic variables used in this study were household income, race/ethnicity, and educational attainment. Household income is imputed by modeling a variety of factors including age, occupation, home ownership, and median income from several sources including a survey of a nationally representative sample of 150,000 individual households, consumer survey data, consumer product registrations, and ZIP-code level income data from the Internal Revenue Service. Approximately 30% of the race/ethnicity data are collected directly from public records (e.g. driver's license records), while the remaining data are imputed using commercial software[22] that uses algorithms developed with Census data ZIP codes (ZIP+4) and first and last names. This imputation method has been validated and has demonstrated 97% sensitivity, 48% specificity and 71% positive predictive value for estimating the race of Black individuals.[23] Individuals in the database categorized as "other/unknown" for race/ethnicity were those whose race/ethnicity could not be assigned by the imputation algorithm or were added to the dataset after the imputation had been performed. Education level of individuals is derived from the median education level from Census data at the ZIP+4 level. If Census data are missing, education level is coded as unknown.

Rates of missing data vary depending on the specific study population, the specific data elements used and the year, although the completeness of the sociodemographic information available has improved over time. For example, in 2008, household income, race/ethnicity and education were populated for 54%, 59% and 62% of the claims population, respectively; in 2010, these variables were populated for 63%, 68%, and 71%, respectively; and in 2012, they were populated for 81%, 96% and 97%, respectively.

The sociodemographic database is refreshed quarterly. Data used for this study were based on the most recent refresh available to Optum, which varied from May 2007 through May 2013 (when the data were extracted) for any individual subject. Depending on whether a subject's information

changed between refreshes, the effective dates for the sociodemographic information used in this study may have been earlier than the latest refresh date and also varied by subject.

B. Study Reviews

1. Institutional Review Board (IRB) Review

Optum submitted the Vaccination study protocol and a request for exemption review to the New England Institutional Review Board (NEIRB). In November 2013, NEIRB exempted this portion of the study from IRB review. The study was eligible for exemption under Category E (research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available OR if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects).

2. Optum Disclosure Limitation Program

Optum has implemented a Disclosure Limitation Process as part of its overall privacy initiative in order to comply with applicable privacy laws and best business practices in protecting sensitive data that are in Optum custody. Optum's Disclosure Limitation Program allows Optum to comply with the Privacy Rule adopted by the U.S. Department of Health and Human Services under the Health Insurance Portability and Accountability Act (HIPAA). In situations where the Privacy Rule does not allow use of protected health information (PHI), the Privacy Rule does allow de-identification of the PHI. Once de-identified, PHI is no longer subject to the Privacy Rule, and can be used or disclosed without limitation as long as it is not re-identified. Optum has worked with recognized industry experts on de-identification methodology to comply with HIPAA Privacy requirements and developed a "Statistical Alternative Methodology" for de-identification of data. In May 2013, disclosure analysis of the Vaccination study data was completed under Optum's Disclosure Limitation Program, and it was determined that the data has been de-identified as required under applicable law and that there is a minimal risk of re-identification.

No patient's identity or medical records was or will be disclosed for the purposes of this study except in compliance with applicable law.

C. Study Sample

The study samples for the analyses presented both in Report 1 and herein were identified from the same initial subject population. Different analyses required different subsets of the initial subject population; consequently, the description below begins with the initial study population, also described in Report 1.

1. Subject Identification

The study sample (A1*)[ii] included infants ("**index children**") in the ORD born between 01 January 2001 and 31 December 2011 ("**index child identification [ID] period**") who were

[ii] The A1* sample is a subset of the A1 sample described in Report 1, and the "*" denotation is retained throughout this report for consistency with Report 1.

continuously enrolled in the commercial health plan from birth to at least 8 months (245 days) of age, and who also had an older sibling continuously enrolled in the health plan for at least 6 months (182 days) between 1 January 1997 and 31 December 2012 ("**older sibling ID period**").

a. Inclusion Criteria

To be included in the study sample (A1*), index children met the following inclusion criteria:

- Born during the index child ID period (01 January 2001 through 31 December 2011);
- Enrolled in a commercial health plan with medical and pharmacy coverage within 32 days of birth;
- Continuously enrolled in a commercial health plan with medical and pharmacy coverage from birth to at least 8 months of age[iii], between 01 January 2001 and 31 December 2012 ("**study period**");[iv] and
- Had an older sibling continuously enrolled in the health plan with medical and pharmacy coverage for at least 6 months during the older sibling ID period (01 January 1997 through 31 December 2012)
    - As in the previous study, we identified siblings of index children using a unique system-generated family identifier variable. We determined whether each identified index child had at least one family identification (ID) value. If an index child had more than one family ID, we used all family IDs associated with each index child to identify older siblings. Older siblings of index children were identified according to the algorithm shown below. Index children were required to have at least one older sibling enrolled in the health plan, but were not required to have a parent enrolled in the health plan.

Table 1. Algorithm for Identifying Family Members

Age Difference	Family Member Assignment
Family member is 0.5-17 years older than index child	Older Sibling
Family member is female and 18-49 years older than index child	Mother
Family member is male and 18-49 years older than index child	Father
Family member is 50 or more years older than index child	Not applicable (assumed grandparent)

    - Each older sibling was categorized as having "likely" ASD, "possible" ASD or no ASD. ASD was identified with the ICD-9-CM codes shown in the table below.

[iii] Continuous enrollment from birth to 8 months of age is required in order to capture the complete vaccination windows for the first three doses of the Hib, PCV and rotavirus vaccines.

[iv] Truncating the ID period at December 2011 excludes a small subset of children from our A1 sample – specifically, those index children born between January and April 2012 who have eight or more months of continuous enrollment through December 2012, however we limited our ID period to 2011 to allow for full year of birth comparisons, if required.

Table 2. Codes for Identifying Autism Spectrum Disorders

Condition	ICD-9 CM Dx
Autism	299.0x
Asperger's disorder	299.8x
Unspecified Pervasive Development Disorder (PDD)	299.9x

- "Likely" ASD was defined as at least two medical claims with ICD-9-CM diagnosis codes indicating ASD on separate days; diagnosis codes could be primary or secondary, i.e., in any position on the medical claim.
- "Possible" ASD was defined as one medical claim with a primary or secondary diagnosis code for ASD.
- No ASD meant that the older sibling had no medical claims with ASD-related diagnosis codes.

- Had at least one older sibling with likely ASD, ***or*** all older siblings had no ASD. Index children with an older sibling identified as having possible ASD, but with no older siblings with likely ASD were excluded from the final study population. [v]

2. Analytic Subgroups

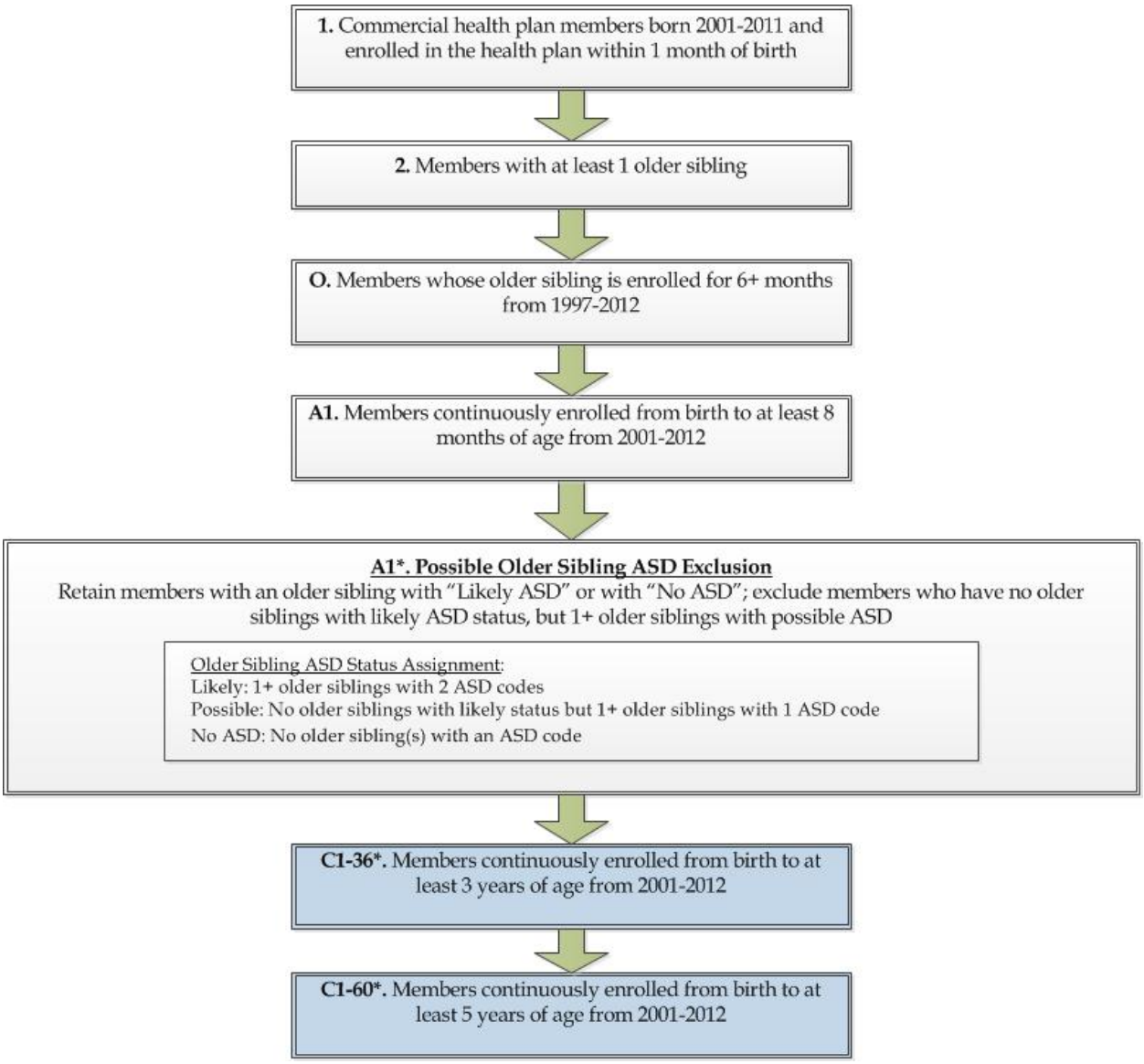
In addition to the overall (A1*) sample, subgroups were identified for the analyses presented in this report to address the research questions (Figure 1).

- **C1-36*:** The C1-36* subset included index children continuously enrolled with medical and pharmacy coverage from birth to at least 36 months (1096 days) of age to evaluate the relationship between vaccination status and vaccine-related infectious disease; and
- **C1-60*:** The C1-60* subset included index children continuously enrolled with medical and pharmacy coverage from birth to at least 60 months (1827 days) of age to evaluate the relationship between MMR vaccination status and ASD/neurodevelopmental health outcomes.

Figure 1 presents the identification of the initial study population and all analysis samples.

[v] The medical chart validation study we completed in the initial portion of this project demonstrated that requiring at least 2 claims with primary or secondary ASD diagnoses on separate dates ("likely ASD") generated a positive predictive value approaching 90%. The less restrictive criterion of at least one medical claim with a primary or secondary ASD diagnosis code (combining "possible" and "likely" ASD categories) had a lower positive predictive value of 74%. We therefore decided to limit older siblings to those with "likely" ASD to avoid potential misclassification; consequently, we excluded otherwise eligible index children with older siblings with "possible" ASD from our study samples.

Figure 1. Sample and Subgroup Inclusion Criteria and Labels



3. Observation Period

Infants born during the index child ID period (01 January 2001 to 31 December 2011) with at least 8 months of continuous enrollment were included as index children. The index child's date of birth was set as the index date, and the number of days of continuous enrollment with simultaneous medical and pharmacy coverage from each index child's date of birth was calculated. Continuous enrollment was defined as enrollment up until disenrollment (i.e., a gap in enrollment of more than 32 days). If the enrollment period extended past 31 December 2012, continuous enrollment was truncated at 31 December 2012. Only the first continuous enrollment period (i.e., the period from the date of birth to the first gap of enrollment) was included as observation time for the index children. Additional enrollment periods (if they existed) were not included. Index children were observed for a variable period of time, however at minimum, all index children were observed from 0-36 months

for the analyses presented in this report. A subset of index children with at least 60 months of continuous enrollment was identified for a subset of analyses.

Eligible older siblings were observed for at least 6 continuously enrolled months between 01 January 1997 and 31 December 2012. All available observation time for eligible older siblings was used, regardless of continuous enrollment, to determine the ASD status of the older sibling.

D. Variable Definitions

1. *Index Child Enrollment and Health Coverage Characteristics*

- **Total enrollment time during study.** The sum of the number of days of enrollment during the continuous enrollment period.
- **Mental health coverage enrollment.** Mental health coverage indicated that mental health services were managed as part of a carve-out plan rather than as part of the medical plan. Continuous mental health care coverage was not an inclusion criterion. Index children with continuous enrollment with carved-out mental health care services (as opposed to part of the medical plan) were identified with a binary indicator variable and this variable was included as a covariate in some of the multivariable analyses, when it was believed to be a potential confounder.
- **Enrolled from birth to 3 years of age.** Whether the index child was continuously enrolled in the health plan with medical and pharmacy coverage from birth to 3 years (1096 days) of age.
- **Enrolled from birth to 5 years of age.** Whether the index child was continuously enrolled in the health plan with medical and pharmacy coverage from birth to 5 years (1827 days) of age.

2. *Index Child Demographic Characteristics*

- **Birth year.** The index child's year of birth.
- **Gender.** Gender from enrollment data.
- **Race/ethnicity.** Available categories included: White, African-American/Black, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, Asian, Hispanic or other. Because of smaller sample sizes, Native Hawaiian or Pacific Islander and American Indian or Alaskan Native were combined with the other category to form a combined "other" category. This variable depended on the successful linkage with and the availability of information within the socioeconomic database. Data were therefore missing for some study subjects. Subjects with missing data were categorized as "unknown."
- **Geographic location.** The United States region in which the index child was located in a health plan as of the index date. States were categorized into four geographic regions in accordance with the U.S. Census Bureau's region designations. The regions are presented below in Table 3.

Table 3. Geographic Regions

Census Region	Census Division	State
Northeast	New England	CT MA ME NH RI VT
	Mid Atlantic	NJ NY PA
Midwest	East North Central	IL IN MI OH WI
	West North Central	IA KS MN MO ND NE SD
South	South Atlantic	DC DE FL GA MD NC SC VA WV
	East South Central	AL KY MS TN
	West South Central	AR LA OK TX
West	Mountain	AZ CO ID MT NM NV UT WY
	Pacific	AK CA HI OR WA
Other	Other	Armed Forces, American Samoa, Federated State of Micronesia, Guam, Marshall Islands, Commonwealth of the Northern Mariana Islands, Puerto Rico, Palau, Virgin Islands

3. Vaccination Characteristics

Vaccination variables were created for each index child using information from their entire enrollment period.

- ***Haemophilus influenzae* type B (Hib) vaccinations.** The number, type of vaccination (PRP-OMP; polyribosylribitol phosphate polysaccharide conjugated to a meningococcal outer membrane protein [CPT 90647, 90748], PRP-T; polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid [CPT 90644, 90648, 90698, 90721] or other unspecified Hib vaccine [CPT 90645, 90646, 90720, 90737]) and age at vaccination for each dose of Hib vaccine administered.[vi] Vaccinations administered either prior to the minimum acceptable age[vii], or too close to a previous vaccination dose were considered invalid and not counted.[24]
- **Conjugate pneumococcal (PCV) vaccinations.** The number, type (PCV-7 [CPT 90669], PCV-13 [CPT 90670] or unspecified PCV [HCPCS S0195]) and age at vaccination for each dose of PCV vaccine administered. Vaccinations administered either prior to the minimum acceptable age, or too close to a previous vaccination dose were considered invalid and not counted.[24]
- **Rotavirus (RV) vaccinations.** The number, type (RV1 [CPT 90861] or RV5 [CPT 90860]) and age at vaccination for each dose of RV vaccine administered. Vaccinations administered either prior to the minimum acceptable age, or too close to a previous vaccination dose were considered invalid and not counted. [24]
- **Hib/PCV/RV composite completion.** An indicator variable to measure complete vaccination status (for each vaccine of interest) by 24 months of age

[vi] Note, if the first dose is administered at age 7 months or later, fewer doses are required. http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf

[vii] If the first dose in a series is given ≥5 days before the recommended minimum age, the dose should be repeated on or after the date when the child reaches at least the minimum age.

(3/4Hib+4PCV+2/3RV). Completion was determined based on the number of doses administered and the type of vaccine administered. For example, a Hib series that included 1 or more doses of PRP-T required 4 doses by 24 months to be considered complete, whereas a Hib series containing all doses of PRP-OMP required 3 doses by 24 months to be considered complete. Similarly, an RV series that contained at least 1 dose of RV-5 required 3 doses to be considered complete, whereas an RV series containing all doses of RV-1 required only 2 doses to be considered complete. We also captured the age of the index child when all 3 vaccination series were complete. If the index child did not complete all 3 vaccination series by the end of their follow-up period, this variable was set to missing.

- **Measles vaccination.** The number and age at vaccination for each dose of measles vaccine administered (Table 4). Vaccinations administered either prior to the minimum acceptable age, or too close to a previous vaccination dose were considered invalid and not counted. [24]
- **Mumps vaccination.** The number and age at vaccination for each dose of mumps vaccine administered (Table 4). Vaccinations administered either prior to the minimum acceptable age, or too close to a previous vaccination dose were considered invalid and not counted. [24]
- **Rubella vaccination.** The number and age at vaccination for each dose of rubella vaccine administered (Table 4). Vaccinations administered either prior to the minimum acceptable age, or too close to a previous vaccination dose were considered invalid and not counted. [24]
- **MMR vaccination completion.** An indicator variable to measure complete first MMR vaccination status (i.e., at least one dose between 12 and 24 months of age). MMR completion was determined according to the algorithm provided in Table 4. In addition, we captured the age of the index child when the first dose of the MMR series was administered/completed. If components of the MMR vaccine were administered separately, we captured the age of the child when all three components were administered.
- **Number of MMR doses.** The number of MMR doses administered during the entire enrollment period was captured as 0, 1 or 2. The age at vaccination for each dose was also captured. MMR vaccination was determined according to the algorithm provided in Table 4.

Table 4. Codes for Identifying MMR Vaccination[viii]

Criteria		Code	Code Type	Description	
A	1	90704	CPT	Mumps virus vaccine, live, for subcutaneous use	OR
		99.46	ICD-9 proc	Vaccination against mumps	
	AND				
	2	90705	CPT	Measles virus vaccine, live, for subcutaneous use	OR
		99.45	ICD-9 proc	Vaccination against measles	
	AND				
	3	90706	CPT	Rubella virus vaccine, live, for subcutaneous use	OR
		99.47	ICD-9 proc	Vaccination against rubella	
OR					
B	1	90704	CPT	Mumps virus vaccine, live, for subcutaneous use	OR
		99.46	ICD-9 proc	Vaccination against mumps	
	AND				
	2	90708	CPT	Measles and rubella virus vaccine, live, for subcutaneous use	
OR					
C	1	90705	CPT	Measles virus vaccine, live, for subcutaneous use	OR
		99.45	ICD-9 proc	Vaccination against measles	
	AND				
	2	90709	CPT	Rubella and mumps virus vaccine, live, for subcutaneous use	
OR					
D	1	90707	CPT	Measles, mumps and rubella virus vaccine (MMR), live, for subcutaneous use	OR
		99.48	ICD-9 proc	Administration of measles-mumps-rubella vaccine	
OR					
E	1	90710	CPT	Measles, mumps, rubella, and varicella vaccine (MMRV), live, for subcutaneous use	

4. Clinical Characteristics

Infectious disease outcome variables were created for each index child during their entire enrollment period. For otitis media, pneumonia and meningitis, multiple episodes of illness were captured for each index child.

- **Otitis media.** Whether or not the index child had an episode of otitis media (Table 5) was determined. The number of episodes, the index child's age at the start of each episode,

[viii] To meet the A criteria, individuals must have claims with: 1) either CPT code 90704 *or* ICD-9 procedure code 99.46; and 2) either CPT 90705 *or* ICD-9 proc 99.45; and 3) either CPT 90706 *or* ICD-9 proc 99.47. To meet the B criteria, individuals must have claims with: 1) either CPT 90704 *or* ICD-9 proc 99.46; and 2) CPT 90708. To meet the C criteria, individuals must have claims with: 1) CPT 90705 *or* ICD-9 proc 99.45; and 2) CPT 90709. To meet the D criteria, individuals must have a claim with CPT 90707 or ICD-9 proc 99.48. To meet the E criteria, individuals must have a claim with CPT 90710.

and number of days' duration for each episode were determined. The end of each episode was identified by a gap of 30 days without codes indicating otitis media. The end of each episode was set as the beginning of the 30-day gap in otitis media claims or as the end of follow-up, whichever occurred first.

Table 5. Codes Indicating Otitis Media

Code	Description
381.3	Other and unspecified chronic nonsuppurative otitis media
381.4	Nonsuppurative otitis media, not specified as acute or chronic
381.0	Acute nonsuppurative otitis media
381.1	Chronic serous otitis media
381.2	Chronic mucoid otitis media
382.x	Suppurative and unspecified otitis media
382.1	Chronic tubotympanic suppurative otitis media
382.3	Unspecified chronic suppurative otitis media
382.9	Unspecified otitis media
382.4	Unspecified suppurative otitis media
382.0	Acute suppurative otitis media
382.2	Chronic atticoantral suppurative otitis media

- **Pneumonia.** Whether or not the index child had an episode of pneumonia (Table 6) was determined. The number of episodes, the index child's age at the start of each episode, and number of days' duration for each episode were determined. The end of each episode was identified by a gap of 30 days without codes indicating pneumonia. The end of each episode was set as the beginning of the 30-day gap in pneumonia claims or as the end of follow-up, whichever occurred first.

Table 6. Codes Indicating Pneumonia

Code	Description
481	Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia)
482.2	Pneumonia due to *Haemophilus influenzae* (*H. influenzae*)
482.3	Pneumonia due to Streptococcus
482.8	Pneumonia due to other specified bacteria
482.9	Unspecified bacterial pneumonia
483.8	Pneumonia due to other specified organism
484.8	Pneumonia in other infectious diseases classified elsewhere
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified

- **Meningitis.** Whether or not the index child had an episode of meningitis (Table 7) was determined. The number of episodes, the index child's age at the start of each episode, and number of days' duration for each episode will be determined. The end of each episode was identified by a gap of 30 days without codes indicating meningitis. The end of each episode was set as the beginning of the 30-day gap in meningitis claims or as the end of follow-up, whichever occurred first.

Table 7. Codes Indicating Meningitis

Code	Description
320.0	Haemophilus meningitis
320.1	Pneumococcal meningitis
320.2	Streptococcal meningitis
320.7	Meningitis in other bacterial diseases classified elsewhere
320.8	Meningitis due to other specified bacteria
320.9	Meningitis due to unspecified bacterium
322.2	Chronic meningitis
322.9	Unspecified meningitis

- **Gastroenteritis.** Whether or not the index child had an episode of gastroenteritis (Table 8) was determined. The number of episodes, the index child's age at the start of the episode, and number of days' duration for each episode were determined. The end of each episode was identified by a gap of 30 days without codes indicating gastroenteritis. The end of each episode was set as the beginning of the 30-day gap in gastroenteritis claims or as the end of follow-up, whichever occurred first.

Table 8. Codes Indicating Gastroenteritis

Code	Description
008.61	Rotavirus
008.69	Other viral enteritis
008.8	Other organism, not elsewhere classified
009.x	Ill-defined intestinal infections
009.0	Infectious colitis, enteritis, and gastroenteritis
009.1	Colitis, enteritis, and gastroenteritis of presumed infectious origin
009.2	Infectious diarrhea
009.3	Diarrhea of presumed infectious origin

- **Measles diagnosis.** Whether or not the index child had a diagnosis for measles (ICD9-CM 055.xx) was determined, and the index child's age at first measles diagnosis was captured.
- **Mumps diagnosis.** Whether or not the index child had a diagnosis for mumps (ICD9-CM 072.xx) was determined, and the index child's age at first mumps diagnosis was captured.
- **Rubella diagnosis.** Whether or not the index child has a diagnosis for rubella (ICD9-CM 056.xx) was determined, and the index child's age at first rubella diagnosis was captured.

Diagnosis codes indicating congenital rubella syndrome (ICD9-CM 771.0) were not included.

- **Measles/mumps/rubella composite outcome.** A composite outcome was created which included measles, mumps, and rubella. Whether or not the index child had a diagnosis for measles (ICD9-CM 055.xx), mumps (ICD9-CM 072.xx) or rubella (ICD9-CM 056.xx) was determined, and the index child's age at earliest diagnosis of any of these conditions was captured.

ASD and other neuropsychiatric conditions outcome variables were created for each index child using information from their entire enrollment period.

- **Index children with likely or possible ASD.** Index children with 2 or more medical claims indicating ASD (Table 2) in any position on separate days during their entire enrollment period were classified as "likely" ASD cases. Index children with only one medical claim for ASD (in any position) were categorized as "possible" ASD cases. For likely and possible ASD cases, the age of the index child at the time of the first ASD claim was captured.
- **Neuropsychiatric conditions other than ASD.** Index children with at least one medical claim during their entire enrollment period with an ICD-9-CM diagnosis code, in any position on the claim, indicating a neuropsychiatric condition were identified with a dichotomous indicator variable; see Table 9.

Table 9. Codes for Identifying Neuropsychiatric Conditions

ICD-9 code	Diagnosis Label
307.20-307.22[ix]	Tic disorder, unspecified; transient tic disorder; chronic motor or vocal tic disorder
307.3	Stereotypic movement disorder
313.2x[x]	Sensitivity, shyness, social withdrawal disorder,
315.xx[xi]	Specific delays in development
317-319	Mental retardation
307.3	Stereotypic movement disorder
348.30	Static encephalopathy
781.8	Sensory integration dysfunction
783.42	Delayed developmental milestones
784.41	Aphonia
784.42	Dysphonia
784.51	Dysarthria
784.52	Fluency disorder in conditions classified elsewhere
784.59	Other speech disturbance
784.6x	Other symbolic dysfunction
V40.0	Problems with learning
V40.1	Problems with communication (including speech)
V61.20	Problem concerning behavior of a child

[ix] Excludes 307.23 which is Tourette's syndrome.
[x] Includes: 313.22, introverted disorder of childhood; and 313.23, selective mutism.
[xi] Inclusive of all 315.xx; a few may not be relevant but are unlikely to be used in very young children.

Our multivariable analyses examining the outcome of vaccination status included measures of clinical characteristics that are potential vaccination contraindications or reasons for delay/avoidance of vaccination.

- **Seizures.** Whether or not the index child had evidence of epilepsy and recurrent seizures (ICD-9-CM 345.xx) or convulsions (ICD-9-CM 780.3x), which may be cited as a contraindication for vaccination. A binary indicator (yes/no) was created to identify children with at least one medical claim with a relevant diagnosis code in any position from birth to 24 months of age. In addition, the age of the index child at first evidence of seizure using data from their entire enrollment period was also captured for inclusion in the multivariable analysis as a time-varying covariate.
- **Vaccination-related allergies.** Whether or not the index child had evidence of a severe allergy or an allergy that might be associated with vaccination, which may be a contraindication for vaccination. A binary indicator variable (yes/no) was created to identify index children with at least one medical claim with a relevant diagnosis code (Table 10) in any position from birth to 24 months of age. In addition, the age of the index child at first evidence of relevant allergies using data from their entire enrollment period was also captured for inclusion in the multivariable analysis as a time-varying covariate.

Table 10. Codes Indicating Allergic Contraindications to Vaccinations

ICD-9 Dx Code	Condition
995.68	Anaphylactic reaction due to eggs
999.39	Complications of medical care, NEC, infection following other infusion, injection, transfusion, or vaccination
999.42	Anaphylactic reaction due to vaccination
E948.4	Tetanus vaccine causing adverse effect in therapeutic use
E948.5	Diphtheria vaccine causing adverse effect in therapeutic use
E948.6	Pertussis vaccine, including combinations with pertussis component, causing adverse effect in therapeutic use
E948.8	Other and unspecified bacterial vaccines causing adverse effect in therapeutic use
E948.9	Mixed bacterial vaccines, except combinations with pertussis component, causing adverse effect in therapeutic use
E949.4	Measles vaccine causing adverse effect in therapeutic use
E949.5	Poliomyelitis vaccine causing adverse effect in therapeutic use
E949.6	Other and unspecified viral and rickettsial vaccines causing adverse effect in therapeutic use
E949.7	Mixed viral-rickettsial and bacterial vaccines, except combinations with pertussis component, causing adverse effect in therapeutic use
E949.9	Other and unspecified vaccines and biological substances causing adverse effect in therapeutic use
V14.7	Personal history of allergy to serum or vaccine
V15.03	Personal history of allergy to eggs
V64.04	Vaccination not carried out because of allergy to vaccine or component

- **Pre-term birth.** Whether or not the index child had evidence of prematurity, which could be associated with vaccination timing as well as medical complexity. Children with at least one medical claim with a relevant diagnosis code indicating prematurity, fetal

immaturity, low birth weight or <36 weeks of gestation (see Table 11) in any position were identified with a binary (yes/no) indicator variable. Note that some indicators of prematurity may only be recorded in the mother's health care claims but, for this study, mothers' claims were not examined.

Table 11. Codes Indicating Pre-term Birth

ICD-9 Dx Code	Description
362.20	Retinopathy of prematurity, unspecified
362.22	Retinopathy of prematurity, stage 0
362.23	Retinopathy of prematurity, stage 1
362.24	Retinopathy of prematurity, stage 2
362.25	Retinopathy of prematurity, stage 3
362.26	Retinopathy of prematurity, stage 4
362.27	Retinopathy of prematurity, stage 5
765.00	Extreme fetal immaturity, unspecified (weight)
765.01	Extreme fetal immaturity, less than 500 grams
765.02	Extreme fetal immaturity, 500-749 grams
765.03	Extreme fetal immaturity, 750-999 grams
765.04	Extreme fetal immaturity, 1,000-1,249 grams
765.05	Extreme fetal immaturity, 1,250-1,499 grams
765.06	Extreme fetal immaturity, 1,500-1,749 grams
765.07	Extreme fetal immaturity, 1,750-1,999 grams
765.08	Extreme fetal immaturity, 2,000-2,499 grams
765.09	Extreme fetal immaturity, 2,500 or more grams
765.10	Other preterm infants, unspecified (weight)
765.11	Other preterm infants, less than 500 grams
765.12	Other preterm infants, 500-749 grams
765.13	Other preterm infants, 750-999 grams
765.14	Other preterm infants, 1,000-1,249 grams
765.15	Other preterm infants, 1,250-1,499 grams
765.16	Other preterm infants, 1,500-1,749 grams
765.17	Other preterm infants, 1,750-1,999 grams
765.18	Other preterm infants, 2,000-2,499 grams
765.19	Other preterm infants, 2,500 or more grams
765.21	Less than 24 completed weeks of gestation
765.22	24 completed weeks of gestation
765.23	25-26 completed weeks of gestation
765.24	27-28 completed weeks of gestation
765.25	29-30 completed weeks of gestation
765.26	31-32 completed weeks of gestation
765.27	33-34 completed weeks of gestation
765.28	35-36 completed weeks of gestation

ICD-9 Dx Code	Description
776.6	Anemia of neonatal prematurity
V21.30	Low birth weight status, unspecified
V21.31	Low birth weight status, less than 500 grams
V21.32	Low birth weight status, 500-999 grams
V21.33	Low birth weight status, 1000-1499 grams
V21.34	Low birth weight status, 1500-1999 grams
V21.35	Low birth weight status, 2000-2500 grams

- **Childhood Chronic Conditions Score (modified).** There is currently no comorbidity measure for children that has been externally validated for use in administrative data. Comorbidities indicate complexity of health status that may have had an impact on our study outcomes independent of vaccination status. To capture clinical comorbidity (i.e., complexity) for the index children in our study, we calculated a comorbidity score modeled after the Childhood Chronic Conditions (CCC) score by Feudtner.[25] We modified the CCC by using the diagnosis codes from medical claims for each index child to create a score. Diagnosis codes directly related to ASD were also removed from the modified score. We created the modified CCC comorbidity measures for index children based on the presence of diagnosis codes for CCC conditions on medical claims from birth to 24 months. For each subject, a dichotomous flag (0/1) was created for each of 9 categories of chronic conditions: 1) neuromuscular, 2) cardiovascular, 3) respiratory, 4) renal, 5) gastrointestinal, 6) hematologic or immunologic, 7) metabolic, 8) other congenital or genetic defect, and 9) malignant neoplasms. (In addition, specific conditions within the neuromuscular and metabolic categories were also identified). For each category, a child was coded 1 if he or she had at least one claim for a diagnosis in any position for a condition within each category. These flags were then summed, which resulted in a possible score ranging from 0 to 9 (increasing clinical complexity or comorbidity). While the results of this score were in line with expectations, it is important to acknowledge that the measure has not been formally validated for claims analysis. The relevant ICD-9-CM codes are presented in Table 12.

Table 12. Codes for the Overall Comorbidity Score for Children

Condition		ICD-9 Dx Codes
1	**Neuromuscular**	
	Brain and spinal cord malformations	740.0x - 742.9x
	Intellectual disability	318.0x - 318.2x
	Central nervous system degeneration and disease	330.0x - 330.9x
		334.0x - 334.2x
		335.0x - 335.9x
	Infantile cerebral palsy	343.0x - 343.9x
	Muscular dystrophies and myopathies	359.0x - 359.3x
	Epilepsy and seizure disorders	345.0x - 345.9x

	Condition	ICD-9 Dx Codes
2	**Cardiovascular**	
	Heart and great vessel malformations	745.0x - 747.0x
	Cardiomyopathies	425.0x - 425.4x
		429.1x
	Conduction disorders	426.0x - 427.4x
	Dysrhythmias	427.6x - 427.9x
3	**Respiratory**	
	Respiratory malformations	748.0x - 748.9x
	Chronic respiratory disease	770.7x
	Cystic fibrosis	277.0x
	Asthma	493.0x - 493.9x
4	**Renal**	
	Congenital anomalies	753.0x
	Chronic renal failure	585.xx
5	**Gastrointestinal**	
	Congenital anomalies	750.3x
		751.1x-751.3x
		751.6x - 751.9x
	Chronic liver disease and cirrhosis	571.4x - 571.9x
	Inflammatory bowel disease	555.0x - 556.9x
6	**Hematologic or immunologic**	
	Sickle cell disease	282.5x - 282.6x
	Hereditary anemias	282.0x - 282.4x
	Hereditary immunodeficiency	279.00 - 279.9x
		288.1x - 288.2x
		446.1x
	Acquired immunodeficiency	042.0x - 042.1x
7	**Metabolic**	
	Amino acid metabolism	270.0x - 270.9x
	Carbohydrate metabolism	271.0x - 271.9x
	Lipid metabolism	272.0x - 272.9x
	Storage disorders	277.3x
		277.5x
	Other metabolic disorders	275.0x - 275.3x
		277.2x
		277.4x
		277.6x
		277.8x - 277.9x
	Diabetes	249.xx
		250.xx

	Condition	ICD-9 Dx Codes
8	**Other congenital or genetic defect**	
	Chromosomal anomalies	758.0x - 758.9x
	Bone and joint anomalies	259.4x
		737.3x
		756.0x - 756.5x
	Diaphragm and abdominal wall	555.3x
		756.6x - 756.7x
	Other congenital anomalies	759.7x - 759.9x
9	**Malignant neoplasms**	
	Malignant neoplasms	140.0x - 208.9x
		235.0x - 239.9x

5. *Family Member Characteristics*

Variables that describe the older siblings and parents of index children are listed below. As part of the study inclusion criteria, all index children were required to have at least one older sibling within the research database. Parent measures were created for index children who also had evidence of a parent within the database (see Table 1). In the case where neither a mother nor a father was identified, parent variables were coded as missing.

- **Older sibling characteristics.** For each older sibling, the following information was captured from the administrative claims database:
  - age at index child date of birth
  - gender
  - total CE
  - CE from 12-24 months (yes/no)
  - evidence of ASD (likely, none)
  - among likely ASD, age at first diagnosis code for ASD
- **Mother.** Whether or not the index child's mother was enrolled in the health plan (yes/no) was determined based on the algorithm for identifying family members (Table 1).
  - **Mother's Age.** If the index child's mother was enrolled in the health plan, the age of the mother at the index child's date of birth. Mother's age was categorized as <20, 20-29, 30-34, 35-39, 40-49.
- **Father.** Whether or not the index child's father was enrolled in the health plan (yes/no) was determined based on the algorithm for identifying family members (Table 4).
  - **Father's Age.** If the index child's father is enrolled in the health plan, the age of the father at the index child's date of birth. Father's age was categorized as <29, 30-39, 40-49. For the multivariate models, age was categorized similarly to that of mother's age: <20, 20-29, 30-34, 35-39, and 40-49.
- **Highest maternal/paternal education.** The highest level of maternal or paternal education was captured from the linked sociodemographic data. Available categories

include: <9th grade, 9th grade - <12th grade, high school diploma, some college, Associate degree, Bachelor degree, Master degree, Professional school degree, Doctorate degree. This variable depended on the identification of at least one parent in the database, as well as the successful linkage with and the availability of information within the socioeconomic database. Subjects with some sociodemographic information available but with missing data on both maternal and paternal education were categorized as "unknown." Subjects without any sociodemographic information available were categorized as "no SES information." For the multivariable analyses, the maternal/paternal education classification was further collapsed into a smaller set of categories: <12th grade, high school diploma, some college, Associate degree, Bachelor degree or higher, and unknown (including unknown education, no SES information and no parents identified).

- **Household income.** Modeled household income from the linked socioeconomic data was captured. Available categories included: Under $15,000 , $15,000 - $19,999 , $20,000 - $29,999, $30,000 - $39,999, $40,000 - $49,999, $50,000 - $59,999, $60,000 - $74,999, $75,000 - $99,999, $100,000 - $124,999, $125,000- $149,999, $150,000 - $249,999, $250,000+. For our analyses, these groups were collapsed into a smaller set of 5 categories: <$50,000, $50,000 – $74,999, $75,000 - $99,999, $100,000 - $124,999, and $125,000+. This variable depended on the successful linkage with and the availability of information within the socioeconomic database, however, index children were not required to have a parent identified for this variable to be populated. Data were therefore missing for some study subjects. Index children with some sociodemographic information available but with missing data on household income were categorized as "unknown". Subjects without any sociodemographic information available were categorized as "no SES information." These 2 categories were combined for the multivariable analysis.
- **Older sibling with likely ASD.** The dichotomous indicator variable identified index children with an older sibling with likely ASD. The older siblings considered for this variable were continuously enrolled in the health plan for at least 6 months and had claims indicating likely ASD between 01 January 1997 and 31 December 2012.
- **Age of index child at first evidence of ASD in an older sibling.** If one or more older siblings had evidence of ASD, the index child's age at the time of the first observed diagnosis code for ASD among all older siblings. If there was evidence of ASD in an older sibling prior to the index child's date of birth, then the value was recorded as 0. If there were no older siblings with evidence of ASD, then the value was recorded as missing.[xii]

[xii] There are limitations to this variable because an ASD diagnosis on a claim may not accurately represent the timing of earliest parental concern and diagnosis of ASD in an older sibling. Since a minimum of just 6 months of continuous enrollment was required for older siblings to be included in the study, the study period may not have included enough information to accurately evaluate older sibling ASD status (we may not have observed the older sibling at the time of the ASD diagnosis if they were enrolled in a different health plan or if this time was outside that of the observation period of the study). These limitations should be considered when interpreting this variable and its impact on our results.

IV. Vaccine-related Infectious Disease Outcomes

A. Background

In previous results within the "Health Outcomes Study," children with ASD and their siblings were less likely to be vaccinated with MMR compared to children and siblings without ASD. They also displayed higher rates of infectious disease outcomes, including otitis media, pneumonia, meningitis, and gastroenteritis/diarrhea (see Table 13) when compared to children without ASD and their siblings. Some of these outcomes may be preventable by particular vaccinations that are recommended for children during the first 2 years of life (or "vaccine-related"), specifically the vaccines against rotavirus, pneumococcus and *Haemophilus influenzae* type B (see Table 14 for a list of the organisms addressed by these vaccines and the infectious disease outcomes that are commonly related to these organisms).

Table 13. Prevalence of Vaccine-related Infectious Diseases among Study Samples

Vaccine-related infectious disease	Prevalence rates (%)			
	Children with ASD (N=33,565)	Comparison children (N=138,876)	All siblings of children with ASD (N=41,123)	All siblings of comparison children (N=195,868)
Otitis media	46.01%	27.19%	37.02%	25.03%
Pneumonia	9.55%	4.79%	7.75%	4.66%
Diarrhea/ Gastroenteritis (infectious or presumed infectious)	0.84%	0.30%	0.45%	0.23%
Meningitis	0.21%	0.08%	0.12%	0.10%

Table 14. Organisms addressed via Hib, PCV, RV vaccinations and the common infectious disease manifestations related to these organisms

Organisms	Common infectious disease manifestations
Haemophilus Influenzae type b	Common cause of pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, purulent pericarditis.
Streptococcus pneumoniae (vaccine includes the 7 most prevalent serotypes out of more than 90 serotypes)	Common cause of invasive bacterial infections in children, including febrile bacteremia, acute otitis media, sinusitis, community-acquired pneumonia, pleural empyema, and conjunctivitis.
Rotavirus	Common cause of fever, vomiting, and diarrhea (gastroenteritis), particularly severe in immunocompromised children

Childhood vaccinations have been one of the most important public health developments of the 20th century, resulting in the elimination or near-elimination of many diseases including polio, diphtheria, measles, and mumps.[26,27] Largely resulting from the MMR vaccine, the near-complete elimination of measles, rubella, and congenital rubella in the US was documented by 2004, and shown to be sustained through at least 2011.[28] Because the individual risk of outcomes like measles, mumps and rubella is currently low,[29,30] despite a few well-publicized outbreaks of measles in recent years,[31,32] many parents making individual vaccination decisions for their children may be less concerned about the risk of these rare diseases with which they have no personal experience. However, the persistently low levels of individual risk for these outcomes is

a result of herd immunity - the phenomena that occurs once a sufficient proportion of a population becomes immune that the normal transmission of a disease is impeded. Should increasing numbers of families avoid a vaccination like MMR, herd immunity can be threatened. Moreover, families having children with ASD tend to congregate together, through contact in educational, clinical or community group settings. If these families are more likely to avoid vaccination this could increase the threat to herd immunity within this particular subgroup.

Compared to MMR, the other vaccines we are studying (Hib, PCV, and rotavirus) confer varying and lesser degrees of herd immunity[33] and thus the vaccination status of an individual child could, presumably, predict their infectious outcomes with the relevant organisms. Parents may be unaware of how effective some of these newer vaccines have been in preventing cases of common infectious diseases, including otitis media, pneumonia, and gastroenteritis.[26,33,34,35,36,37] This could be, in part, because these outcomes are caused by a range of infectious agents, both bacterial and viral, and the proportion of these outcomes that is attributable to any one vaccine-preventable cause is variable. Parents' views of the balance between the risks and benefits of vaccines might alter when considering more common infectious outcomes with which they have experience, such as gastroenteritis, otitis media, pneumonia, and, to a lesser extent, meningitis. Showing a positive effect of vaccinating on these outcomes could sway parents toward adhering to the vaccination recommendations from the CDC, especially among parents who are worried about the safety of vaccinations and don't otherwise perceive a benefit.

Thus, we investigated the association between a child's vaccination status and his or her risk of contracting both rare and common infections. We also examined the role of a child's ASD status in relationship to the association between vaccination and infectious disease outcome.

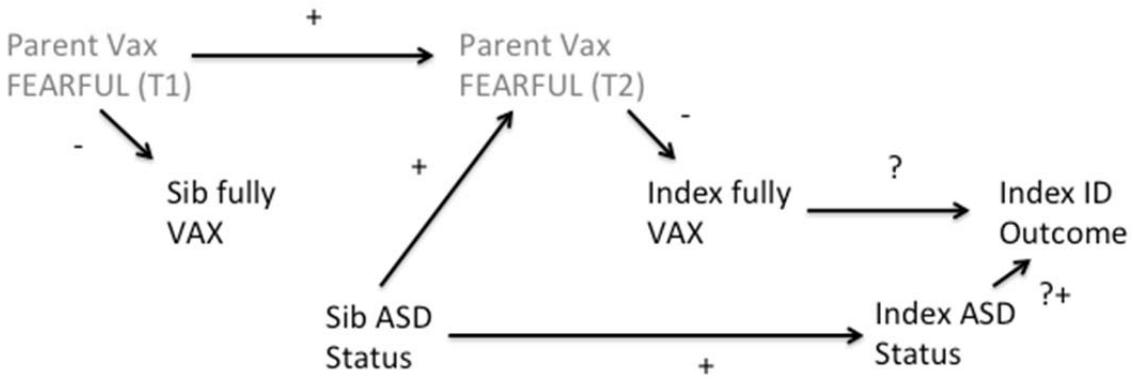
B. Research Questions and Causal Diagram

Our two research questions with respect to the association between index child vaccination status and the risk of vaccine-related infectious diseases are:

1. What is the association between Hib, RV, PCV and MMR vaccination receipt and vaccine-related infectious diseases – including otitis media, pneumonia, meningitis, gastroenteritis, measles, mumps, and rubella among young children?

Does having a diagnosis of ASD confound the relationship between Hib, RV, PCV and MMR vaccination receipt and vaccine-related infectious diseases – including otitis media, pneumonia, meningitis, gastroenteritis, measles, mumps, and rubella? Figure 2 presents the casual diagram for the association between vaccine status and vaccine-related infectious disease outcomes.

Figure 2. Causal Diagram for Vaccine-Related Infectious Disease Health Outcomes



The figure above shows that parent attitudes in a baseline period prior to the time a decision is made to vaccinate an older sibling (T1) will influence the vaccination status of the older sibling and will be associated with parents' attitude at a later time point (T2) when decisions about whether or not to vaccinate a younger sibling need to be made. Parents fearful of vaccine risk at T1 will be less likely to fully vaccinate the older sibling and will be more likely than the average parent to still be vaccine-fearful at T2. These are illustrated by the "-" along the arrow between "Parent VAX Fearful (T1)" and "Older Sib Fully VAX" and the "+" between "Parent VAX Fearful (T1)" and "Parent VAX Fearful (T2)." If, accepting that there is no causal link between older sibling vaccination status and older sibling ASD risk (in either direction), we also allow that the older siblings' ASD status could still influence parental vaccine fearfulness at T2 and assume that this T2 parental vaccine fearfulness will be associated with index children's vaccine status. The principal question at hand is whether the index child's vaccination status influences vaccine-related infectious disease outcomes which we will examine for a range of different vaccines and outcomes as discussed above.

The diagram also shows that older sibling's ASD status is negatively associated with the index child being vaccinated (we saw this empirically in the first portion of this project and we hypothesize in the diagram that this is because ASD-affected older siblings are more likely to have vaccine fearful parents at the time decisions are being made about younger sibling vaccination). The diagram also shows that the older sibling's ASD status is positively associated with index child ASD status (reflecting the recurrence risk which is known to be manifold higher than the baseline population risk). Note, that if the index child's ASD status is itself positively associated with his or her infectious disease outcomes (indicated in the diagram by the arrow with the "?+"), then an unadjusted estimate of the association between index child vaccination status and index child vaccine-related infectious disease outcome could be biased toward the null and the effectiveness of vaccination in preventing infectious disease outcomes would be underestimated. In the previous project we saw consistently higher infectious disease rates in children with ASD compared to comparison children (whether because of some biologic explanation like the existence of some susceptibility factor shared between ASD and infectious disease or due to an artifact such as medical surveillance bias). Therefore, we planned to re-run analyses of index child vaccine status and infectious disease outcomes, adjusting for index child ASD status, in order to control for this potential confound.

C. Analytic Approach

1. Descriptive Analysis

This analysis was conducted on the C1-36* index child subgroup. All variables were analyzed descriptively. Counts and percentages are reported for dichotomous and categorical variables. Means, standard deviations, medians, and ranges are reported for continuous measures. All variables are stratified by index child ASD status: likely, possible, and no ASD. Bivariate comparisons were provided for each pair of mutually exclusive index children: likely ASD versus possible ASD; likely ASD versus no ASD; and possible ASD versus no ASD. The statistical significance of between group differences was tested with two-sided t-tests for continuous variables and with chi-square statistics for categorical variables.

2. Multivariable Regression Analysis

The multivariable analyses to address the research questions regarding vaccination-related infectious disease outcomes examined the associations between vaccination status and the associated infectious disease (i.e., MMR vaccination and measles, mumps or rubella; RV vaccination and gastroenteritis; Hib and PCV vaccination and otitis media, pneumonia and/or meningitis). All regressions were estimated in the C1-36* population, that is, among index children meeting the sample selection criteria who were continuously enrolled from birth through *at least* 36 months of age. Index children had a minimum of 36 months of continuous enrollment, but were followed from birth to the end of their enrollment period (>60 months on average; Table 19) to capture vaccination exposures and outcomes of interest. We limited the gastroenteritis model to observations for index children born during or after 2006 because RV was not FDA approved until 2006.

Because a subject's vaccination status changes over time, and it is also possible for a subject to have more than one event, all multivariable analyses were conducted using Prentice-Williams-Peterson (PWP) stratified Cox models.[38] These models allow the shape of the baseline hazard function to vary across different event episodes accommodating, for example, the fact that the risk of an event can be lower (or higher) for a given second occurrence, compared to that for a first occurrence, at a given age. When there are multiple events, the model accounts for the resulting lack of independence between events occurring in the same index child by employing a robust sandwich covariance estimate when calculating standard errors.[39] As implied here, the time-scale used in these models was the child's age and we used the 'total time' (as opposed to the 'gap time'[40]) approach which means that when a subject has an event, the beginning of the time at risk for subsequent events is the child's chronologic age at that point in follow-up.

Cox models also allow the risk of any infectious disease outcome to change at different ages but assume that the ratio of the hazards across different vaccine exposure groups is constant at different ages. Because this assumption of proportionality of hazards is restrictive, we estimated all of the models with interaction terms between age and vaccination status to test whether the hazard ratios for the risk of infectious disease outcomes changed over time across different vaccination groups. When statistical evidence indicated that the proportionality assumption did not hold for the vaccination effects, we included interaction terms in the final models to estimate separate hazard ratios by age. Note, however, that because our data set is very large, statistically significant differences in hazard ratio estimates at different ages may be quite small. In cases

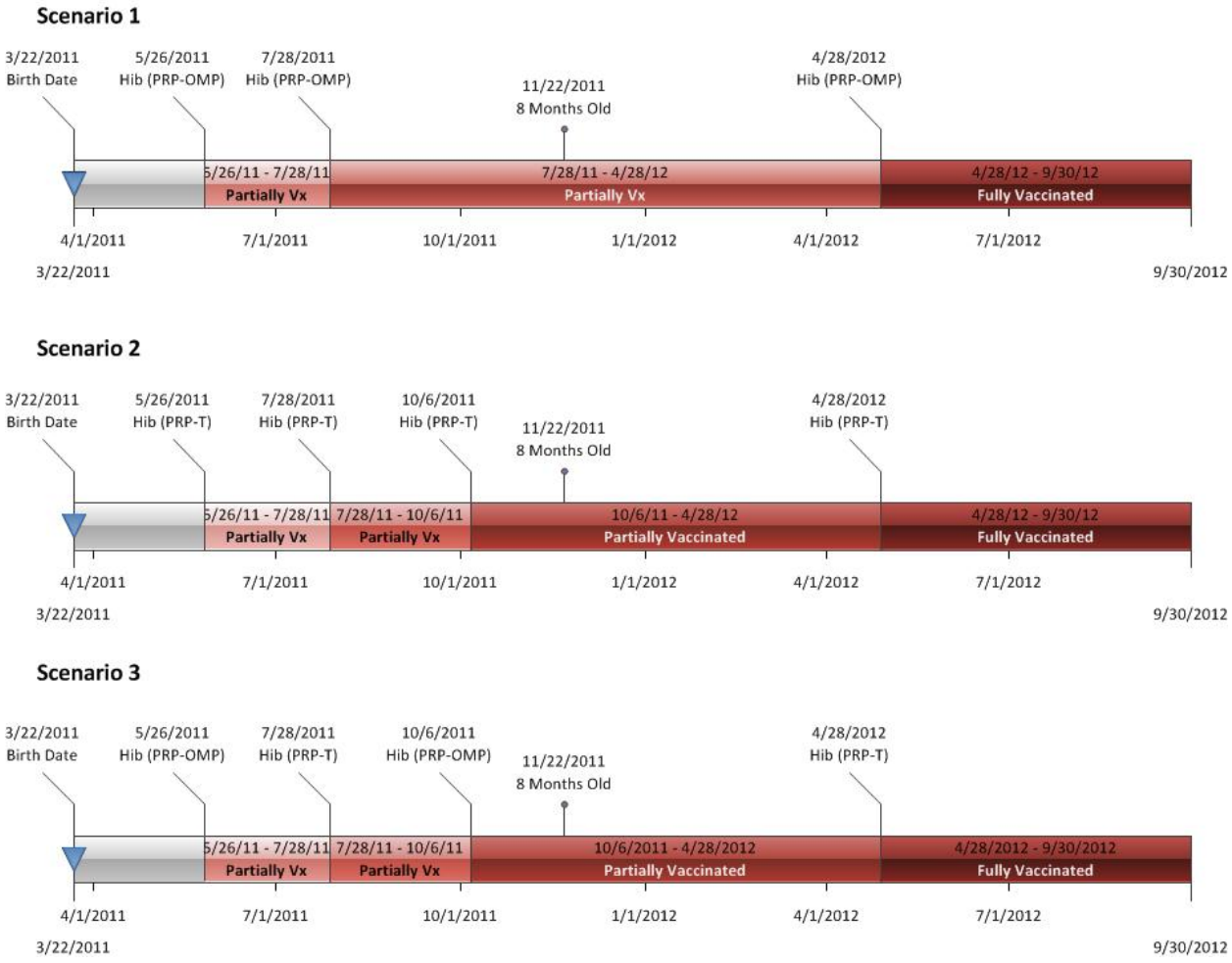
where these were not meaningful from a clinical or public health perspective, we reverted to a simpler model that did not include the interaction term.

Each index child was observed for the outcomes of interest from birth through at least 36 months of age until disenrollment or the end of the study period. As mentioned, vaccination status was included in the models as a time-varying covariate, with categories of unvaccinated, partially vaccinated or fully vaccinated. Index children were considered fully vaccinated with each vaccine when the vaccination series was completed. For the purposes of this analysis:

- MMR was considered complete (for primary series, without booster) after receipt of 1 dose of MMR or equivalent (Table 4);
- RV series was considered complete when the index child received 2 doses of RV-1 or 3 doses of RV-5;
- Hib series was considered complete when the index child received 3 doses of PRP-OMP or 4 doses of PRP-T; and
- PCV series was complete after receipt of 4 doses of PCV7 and/or PCV13.

Mixed series for Hib and RV required the maximum number of doses to be considered complete. As an example, Figure 3 illustrates how estimation of Hib vaccine exposure varies under three different scenarios. Scenario one illustrates a vaccination series where all administered doses are PRP-OMP; scenario two illustrates a vaccination series where all administered doses are PRP-T; and scenario three provides an example of a mixed series comprising doses of both PRP-OMP and PRP-T.

Figure 3. Example of Vaccination Covariate Assignment (Hib)



Inclusion of vaccination exposure in the models as a time-varying covariate essentially defines an index child's vaccination status at every time point (t) between the child's date of birth (t=1) and the end of follow-up. Vaccine doses were parameterized to capture the clinical impact of changing vaccination exposure while making the regression models as parsimonious—and the results as interpretable—as possible The final parameterization for each vaccination in our model-based approaches was as follows:.

- MMR vaccination was classified at each point in time as any MMR vaccine dose or no MMR vaccine doses;
- RV vaccination was classified at each point in time as any RV vaccine doses or no RV vaccine doses; and
- PCV vaccination was classified at each point in time as: (1) unvaccinated for index children with no doses of vaccine; (2) partially vaccinated for index children with 1, 2 or 3 doses of vaccine; and (3) fully vaccinated for index children with 4 doses of vaccine.
- Hib vaccination was classified at each point in time as: (1) unvaccinated for index children with no doses of vaccine; (2) partially vaccinated for index children with at least

one dose of vaccine but fewer doses than required for a complete series; and (3) fully vaccinated for index children with a complete vaccination series.

We estimated unadjusted models for each set of vaccinations and associated infectious disease outcomes, as well as fully adjusted models that accounted for multiple covariates. For each model, additional covariates were finalized based on clinical rationale, descriptive analysis results, and statistical significance. The majority of covariates were time invariant; the exceptions being seizure and vaccine-related allergies. Covariates were not evaluated for proportionality as these covariates served as adjustment variables rather than primary predictors.

In addition to vaccination status, the potential of index child ASD status to confound the relationship between index child vaccination status and the risk of vaccine-related infectious disease outcomes was considered and incorporated into this analysis. To explore this relationship, we estimated separate specifications of each fully adjusted model that included an indicator for possible/likely ASD vs. no ASD.

Table 15 summarizes the various outcomes, independent variables and samples for addressing the research questions.

Table 15. Analysis Summary - Vaccination and Vaccine-related Infectious Diseases

Dependent variable	Primary predictor (time-varying)	Covariates in fully adjusted model	Comment
What is the association between Hib, RV, PCV and MMR vaccination and vaccine-related infectious diseases including otitis media, pneumonia, meningitis, gastroenteritis and measles/mumps/rubella?			
First occurrence of measles, mumps or rubella	MMR vaccination status	Birth year	Vaccination was categorized as not vaccinated for MMR vs. vaccinated for MMR (reference category: ≥ 1 dose) Earlier birth years = older children. Estimated model with interaction between age (time) and MMR vaccination status
Acute gastroenteritis episodes – limited to index children born on or after January 1, 2006*	RV vaccination status	Birth year, gender, US Census region, race/ethnicity, maternal/paternal highest education level, household income, mother's age at index child's birth, father's age at index child's birth, seizure (time-varying), allergies (time-varying), pre-term birth	Vaccination was categorized as no vaccination vs. any vaccination (reference category: ≥ 1 dose). Regression accounted for time-varying vaccination and recurrent gastroenteritis events. Gastroenteritis events were classified as initial or recurrent , which implies a separate hazard function for the first event and all recurrent events Estimated model with interaction between age (time) and RV status
Otitis media episodes	Hib vaccination status, PCV vaccination status	Birth year, gender, US Census region, race/ethnicity, maternal/paternal highest education level, household income, mother's age at index child's birth, father's age at index child's birth, seizure (time-varying), allergies (time-varying), pre-term birth	Hib and PCV vaccinations were categorized as unvaccinated, partially vaccinated, fully vaccinated (reference category: fully vaccinated) Regression accounted for time-varying vaccination and recurrent otitis media events. Estimated model with interactions between age (time) and Hib status and birth year (time) and PCV status.
Pneumonia episodes	Hib vaccination status, PCV vaccination status	Birth year, gender, US Census region, race/ethnicity, maternal/paternal highest education level, household income, mother's age at index child's birth, father's age at index child's birth, seizure (time-varying), allergies (time-varying), pre-term birth	Hib and PCV vaccinations were categorized as unvaccinated, partially vaccinated, fully vaccinated (reference category: fully vaccinated) Regression accounted for time-varying vaccination and recurrent pneumonia events. Estimated model with interactions between age (time) and Hib status and birth year (time) and PCV status.

Dependent variable	Primary predictor (time-varying)	Covariates in fully adjusted model	Comment
Meningitis episodes	Hib vaccination status, PCV vaccination status	Birth year, gender, US Census region, race/ethnicity, maternal/paternal highest education level, household income, mother's age at index child's birth, father's age at index child's birth, seizure (time-varying), allergies (time-varying), pre-term birth	Hib and PCV vaccinations were categorized as unvaccinated, partially vaccinated, fully vaccinated (reference category: fully vaccinated) Regression accounted for time-varying vaccination and recurrent meningitis events. Estimated model with interactions between age (time) and Hib status and birth year (time) and PCV status.
Does having a diagnosis of ASD confound the relationship between Hib, RV, PCV and MMR vaccinations and vaccine-related infectious diseases including otitis media, pneumonia, meningitis, gastroenteritis or measles/mumps/rubella? All models described above were estimated with covariates for fully adjusted models plus index child ASD status (likely/possible ASD vs. No ASD).			

*Note: Gastroenteritis episodes were limited to index children born on or after January1, 2006 because the rotavirus vaccine was not approved by the FDA for use in the United States until February, 2006.

D. Results

1. Sample Identification and Sample Comparison

Table 16 summarizes the results for identification of index children with an older sibling who met the study inclusion criteria described in Section III.C. To select eligible subjects for the study, all children born during the index child ID period (01 January 2001 and 31 December 2011) and enrolled at birth were identified – over 1.5M children. From these, index children with at least one older sibling were flagged, limiting the sample to 870,412 index children, of whom 839,974 had an older sibling who met the minimum six months of CE requirement (Sample O). From this sample, the study subgroups were identified based on index child length of enrollment. The analyses presented in this report focus on Sample C1-36*, which contained 218,647 children and Sample C1-60*, which comprised 96,054 children.

Table 16. Subject Attrition[1]

		Retained		Excluded	
		n	%	n	%
1	Denominator: Index children born from 01 Jan 2001 through 31 Dec 2011, enrolled in the health plan within one month of birth, and with valid gender, geographic region and family ID	1,589,371			
2	Index children with at least one older sibling	870,412	54.76%	718,959	45.24%
O	Index children with at least one older sibling continuously enrolled (CE) with medical and pharmacy (and behavioral health) coverage for at least 6 months from 1997-2012	839,974	96.50%	30,438	3.50%
A1	Index children CE with medical and pharmacy coverage until at least 8 months of age from 2001-2012.	603,999	71.91%	235,975	28.09%
A1*	Retain index children with an older sibling with "Likely ASD" or with "No ASD"; exclude index children who have no older siblings with likely ASD, but 1+ older siblings with possible ASD	601,599	99.60%	2,400	0.40%
C1-36*	Index children CE with medical and pharmacy coverage until at least 3 years of age from 2001-2012.	218,647	65.56%	114,865	34.44%
C1-60*	Index children CE with medical and pharmacy coverage until at least 5 years of age from 2001-2012.	96,054	43.93%	122,593	56.07%

[1] All percentages are relative to the preceding row.

Table 17 provides demographic comparisons between the source population of index children born between 01 January 2001 and 31 December 2011 (i.e., *all* infants born during this time who were enrolled in the health plan), and the samples of index children used for the analyses presented in this report.

The distribution of gender in the study samples were representative of the gender distribution in the source population, with the proportion of females in the samples appearing to be slightly higher than that in the source population. The geographic distribution of the C1-36* and C1-60* samples were similar to the distribution in the source population; the C1-36* and C1-60* samples appeared to have slightly greater representation in the Northeast and Midwest, and slightly lower proportions of index children in the South. Differences in the distribution of characteristics between the source population and the C1-36* and C1-60* populations across birth year occurred

because of the increasingly longer continuous enrollment requirements. White race, income and education were all positively associated with the amount of continuous enrollment in the sample. For example, the proportion of index children from families with a household income greater than $125,000 (the highest income category) was lowest in the source population, higher among index children in the C1-36* sample, and highest in the C1-60* sample.

Table 17. Index Child Demographic Characteristics – Comparison of C1-36* and C1-60* Samples

	(1) All infants (N=1,589,371)		(C1-36*) Infants CE from 0-36 Months w/ an Older Sibling CE ≥6 Months (N=218,647)		(C1-60*) Infants CE from 0-60 Months w/ an Older Sibling CE ≥6 Months (N=96,054)	
	n	%	n	%	n	%
Birth year						
2001	136,048	8.56	21,251	9.72	11,529	12.00
2002	137,827	8.67	21,881	10.01	11,789	12.27
2003	142,733	8.98	22,743	10.40	12,475	12.99
2004	138,763	8.73	22,148	10.13	12,879	13.41
2005	153,392	9.65	24,384	11.15	14,495	15.09
2006	165,934	10.44	25,809	11.80	15,725	16.37
2007	166,744	10.49	27,577	12.61	17,162	17.87
2008	160,972	10.13	26,983	12.34	0	0.00
2009	146,496	9.22	25,871	11.83	0	0.00
2010	122,604	7.71	0	0.00	0	0.00
2011	117,858	7.42	0	0.00	0	0.00
Gender						
Male	819,332	51.55	112,276	51.35	49,130	51.15
Female	770,039	48.45	106,371	48.65	46,924	48.85
Geographic region						
Northeast	172,089	10.83	23,643	10.81	10,610	11.05
Midwest	452,965	28.50	64,228	29.38	28,170	29.33
South	692,178	43.55	93,858	42.93	40,611	42.28
West	271,423	17.08	36,849	16.85	16,631	17.31
Other	716	0.05	69	0.03	32	0.03
Race/Ethnicity						
White	992,229	62.43	158,115	72.32	70,257	73.14
African-American/Black	71,325	4.49	9,612	4.40	3,591	3.74
Native Hawaiian or Pacific Islander	1,358	0.09	186	0.09	82	0.09
American Indian or Alaskan Native	3,161	0.20	476	0.22	192	0.20
Asian	46,429	2.92	7,305	3.34	3,325	3.46
Hispanic	140,429	8.84	20,713	9.47	8,768	9.13
Other	31,486	1.98	3,825	1.75	1,647	1.71
Unknown	99,624	6.27	15,949	7.29	7,598	7.91

	(1) All infants (N=1,589,371)		(C1-36*) Infants CE from 0-36 Months w/ an Older Sibling CE ≥6 Months (N=218,647)		(C1-60*) Infants CE from 0-60 Months w/ an Older Sibling CE ≥6 Months (N=96,054)	
No SES information	203,330	12.79	2,466	1.13	594	0.62
Household income						
Under $50,000	259,052	16.30	33,140	15.16	13,300	13.85
$50,000 - $74,999	345,328	21.73	51,528	23.57	21,903	22.80
$75,000 - $99,999	273,251	17.19	47,867	21.89	21,741	22.63
$100,000 - $124,999	172,556	10.86	34,086	15.59	16,058	16.72
$125,000+	104,477	6.57	24,282	11.11	12,292	12.80
Unknown	231,377	14.56	25,278	11.56	10,166	10.58
No SES information	203,330	12.79	2,466	1.13	594	0.62
Maternal/paternal education						
Less than 12th Grade	21,402	1.35	2,401	1.10	962	1.00
High School Diploma	411,232	25.87	55,974	25.60	23,608	24.58
Some college/ Associate Degree	726,547	45.71	106,750	48.82	46,784	48.71
Bachelor Degree or higher	304,792	19.18	49,380	22.58	23,114	24.06
Unknown	19,510	1.23	2,889	1.32	1,293	1.35
No SES information	103,350	6.50	1,053	0.48	214	0.22
No mothers/fathers identified	2,538	0.16	200	0.09	79	0.08

Comparisons of the initial study population and the O, A1*, B1*, and C1* study samples are provided in Appendix A, Table 1.

2. Patient Characteristics

This section presents the descriptive results of patient characteristics for the C1-36* sample which is the subgroup used for the analysis of vaccination status and vaccine-related infectious disease outcomes. The tables present the characteristics of all index children in the C1-36* as well as stratified by index child ASD status: likely ASD, possible ASD, and without ASD. The narrative focuses on the comparison of index children with likely ASD to index children without ASD.

Table 18 presents demographic characteristics for the C1-36* sample. The distribution of index children over birth years ranged from 6.3% to 14.2% per year in the index child with likely ASD cohort and from 9.7% to 12.6% per year in the index child without ASD cohort. The index child without ASD cohort was more evenly distributed among birth years compared with the index child with likely ASD cohort.

Fifty-one percent (51%) of the sample was male, and there was a notable difference in the proportion of males in the index child with likely ASD cohort (80.9%) relative to the index child with no ASD cohort (51.1%; $p<0.001$), commensurate with the gender distribution among children with ASD (See Task A report) A higher proportion of index children with likely ASD vs. index children without ASD were from the Northeast region (16.9% vs. 10.8%, respectively; $p<0.001$), while relatively fewer of the index children with ASD were from the South (39.9% vs. 42.9% among index children without ASD; $p=0.017$).

The majority of the sample (72%) was White. A slightly larger proportion of index children without ASD were African-American/Black: 4.4% compared with 3.1% of index children with likely ASD (p=0.016). There were no statistically significant differences in the distribution of the other race categories between the index children with likely ASD and those without ASD.

A greater proportion of index children with likely ASD (13.0%) were associated with household incomes higher than $125,000 compared with index children without ASD (11.1%; p=0.020). Conversely, a larger proportion of index children without ASD (15.2%) were associated with household income under $50,000 compared with index children with likely ASD (12.1%; p<0.001). Similarly, the prevalence of at least one parent whose highest level of education was a high school diploma was higher in the cohort of index children without ASD (25.6%) than in the cohort of index children with likely ASD (23.0%; p=0.016), while the prevalence of at least one parent with some college or an Associate degree was higher, at 51.8%, among children with likely ASD compared with 46.5% of index children with possible ASD (p=0.029) and 48.8% of children without ASD (p=0.019).

Index children with likely ASD in the C1-36* sample had longer periods of continuous enrollment, on average, than did index children without ASD (Table 19). Index children with likely ASD were enrolled in their commercial health plans for 2,269 days (6.2 years), on average, compared with the index child without ASD cohort, whose average length of continuous enrollment was 1,925 days (5.3 years; p<0.001). Consequently, higher proportions of the index child with likely ASD cohort had continuous enrollment from birth to 4 years and birth to 5 years relative to the index child without ASD cohort (p<0.001).

Index children's parent characteristics are provided in Table 20. Nearly 91% of index children had exactly one mother identified by the family identification algorithm (refer to Table 1) and 6.9% of index children had more than one potential mother identified. Among index children with just one mother identified in the database, the mother's average age was 32.6±4.6 years; and this differed significantly between index children with likely ASD and index children without ASD (33.4±4.7 years vs. 32.6±4.6 years, respectively; p<0.001). We also calculated average age of mothers including those index children associated with more than one potential mother identified, using the oldest mother's age and the youngest mother's age to provide a range of average mothers' ages. These results were very similar to the mother's average age among index children with only one mother identified; the average age of the oldest potential mothers was 32.8±4.7, and the average age of the youngest potential mothers was 32.3±4.9. In the multivariable analysis, mother's age was categorized: <20, 20-29, 30-34, 35-39, 40-49, multiple (mothers), and unknown categorization.

The age of the index child's father was handled in a similar manner. Overall, 90.1% of index children had exactly one father identified in the database by the family identification algorithm (refer to Table 1), and approximately 4.6% of index children had more than one father identified. Among index children with just one father identified, the father's average age was 34.7±5.2 years; and this differed significantly between index children in the likely ASD cohort compared with those in the without ASD cohort (35.7±5.3 years vs. 34.7±5.2 years, respectively; p<0.001). Estimates for the father's average age including index children with more than one potential father were similar to the father's average age among index children with only one father identified; the average age of the oldest potential fathers was 34.9±5.3, and the average age of the

youngest potential fathers was 34.5±5.4. In the multivariable analysis, father's age was categorized in the same way as was mother's age; those with multiple potential mothers or fathers identified were retained in a separate category.

Table 18. C1-36*[1] Index Child Demographic Characteristics - Index Child w/ ASD vs. No ASD[2]

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Birth year														
2001	21,251	9.72	141	9.04	62	10.56	21,048	9.72	-0.68	0.364	0.84	0.493	-1.52	0.282
2002	21,881	10.01	179	11.47	61	10.39	21,641	10.00	1.48	0.052	0.40	0.749	1.08	0.478
2003	22,743	10.40	192	12.31	58	9.88	22,493	10.39	1.92	0.013	-0.51	0.687	2.43	0.118
2004	22,148	10.13	182	11.67	54	9.20	21,912	10.12	1.55	0.044	-0.92	0.460	2.47	0.103
2005	24,384	11.15	188	12.05	66	11.24	24,130	11.15	0.91	0.257	0.10	0.940	0.81	0.606
2006	25,809	11.80	189	12.12	89	15.16	25,531	11.79	0.32	0.694	3.37	0.012	-3.05	0.061
2007	27,577	12.61	221	14.17	74	12.61	27,282	12.60	1.57	0.064	0.01	0.997	1.56	0.349
2008	26,983	12.34	170	10.90	67	11.41	26,746	12.35	-1.46	0.081	-0.94	0.489	-0.52	0.734
2009	25,871	11.83	98	6.28	56	9.54	25,717	11.88	-5.60	<0.001	-2.34	0.080	-3.26	0.009
2010	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
2011	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
Gender														
Male	112,276	51.35	1,262	80.90	448	76.32	110,566	51.07	29.83	<0.001	25.25	<0.001	4.58	0.019
Female	106,371	48.65	298	19.10	139	23.68	105,934	48.93	-29.83	<0.001	-25.25	<0.001	-4.58	0.019
Geographic region														
Northeast	23,643	10.81	263	16.86	99	16.87	23,281	10.75	6.11	<0.001	6.11	<0.001	-0.01	0.997
Midwest	64,228	29.38	435	27.88	137	23.34	63,656	29.40	-1.52	0.190	-6.06	0.001	4.55	0.034
South	93,858	42.93	623	39.94	269	45.83	92,966	42.94	-3.00	0.017	2.89	0.158	-5.89	0.014
West	36,849	16.85	239	15.32	82	13.97	36,528	16.87	-1.55	0.103	-2.90	0.061	1.35	0.434
Other	69	0.03	0	0.00	0	0.00	69	0.03	-0.03	0.481	-0.03	0.665	–	–

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Race/Ethnicity														
White	158,115	72.32	1,126	72.18	403	68.65	156,586	72.33	-0.15	0.897	-3.67	0.047	3.53	0.108
African-American/ Black	9,612	4.40	49	3.14	35	5.96	9,528	4.40	-1.26	0.016	1.56	0.066	-2.82	0.003
Native Hawaiian or Pacific Islander	186	0.09	0	0.00	1	0.17	185	0.09	-0.09	0.248	0.08	0.483	-0.17	0.103
American Indian or Alaskan Native	476	0.22	1	0.06	2	0.34	473	0.22	-0.15	0.192	0.12	0.527	-0.28	0.126
Asian	7,305	3.34	63	4.04	20	3.41	7,222	3.34	0.70	0.124	0.07	0.923	0.63	0.499
Hispanic	20,713	9.47	151	9.68	61	10.39	20,501	9.47	0.21	0.778	0.92	0.446	-0.71	0.622
Other	3,825	1.75	35	2.24	10	1.70	3,780	1.75	0.50	0.135	-0.04	0.938	0.54	0.436
Unknown	15,949	7.29	123	7.88	52	8.86	15,774	7.29	0.60	0.365	1.57	0.143	-0.97	0.462
No SES information	2,466	1.13	12	0.77	3	0.51	2,451	1.13	-0.36	0.177	-0.62	0.155	0.26	0.522
Household income														
Under $50,000	33,140	15.16	189	12.12	93	15.84	32,858	15.18	-3.06	<0.001	0.67	0.653	-3.73	0.023
$50,000 - $74,999	51,528	23.57	356	22.82	137	23.34	51,035	23.57	-0.75	0.485	-0.23	0.894	-0.52	0.799
$75,000 - $99,999	47,867	21.89	340	21.79	122	20.78	47,405	21.90	-0.10	0.923	-1.11	0.515	1.01	0.611
$100,000 - $124,999	34,086	15.59	267	17.12	95	16.18	33,724	15.58	1.54	0.095	0.61	0.685	0.93	0.607
$125,000+	24,282	11.11	202	12.95	68	11.58	24,012	11.09	1.86	0.020	0.49	0.704	1.36	0.395
Unknown	25,278	11.56	194	12.44	69	11.75	25,015	11.55	0.88	0.278	0.20	0.879	0.68	0.668
No SES information	2,466	1.13	12	0.77	3	0.51	2,451	1.13	-0.36	0.177	-0.62	0.155	0.26	0.522

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Maternal/paternal education														
Less than 12th Grade	2,401	1.10	13	0.83	8	1.36	2,380	1.10	-0.27	0.315	0.26	0.541	-0.53	0.266
High School Diploma	55,974	25.60	358	22.95	152	25.89	55,464	25.62	-2.67	0.016	0.28	0.878	-2.95	0.153
Some college/Associate Degree	106,750	48.82	808	51.79	273	46.51	105,669	48.81	2.99	0.019	-2.30	0.266	5.29	0.029
Bachelor Degree or higher	49,380	22.58	362	23.21	149	25.38	48,869	22.57	0.63	0.551	2.81	0.104	-2.18	0.291
Unknown	2,889	1.32	16	1.03	4	0.68	2,869	1.33	-0.30	0.302	-0.64	0.173	0.34	0.459
No SES information	1,053	0.48	3	0.19	0	0.00	1,050	0.48	-0.29	0.097	-0.48	0.091	0.19	0.288
No mother/father identified	200	0.09	0	0.00	1	0.17	199	0.09	-0.09	0.231	0.08	0.532	-0.17	0.103

[1] The C1-36* subset included index children with ≥ 36 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses on separate dates; Possible ASD – index children with only 1ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 19. C1-36*[1] Index Child Enrollment Characteristics – Index Child w/ ASD vs. No ASD[2]

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	mean	SD	mean	SD	mean	SD	Mean	SD						
Length of continuous enrollment (CE) (years)	5.28	1.99	6.21	2.21	5.75	2.15	5.27	1.98	0.94	<0.001	0.48	<0.001	0.46	<0.001
	n	%	n	%	n	%	N	%						
CE from birth to 4 years of age	145,625	66.60	1,293	82.88	452	77.00	143,880	66.46	16.43	<0.001	10.54	<0.001	5.88	0.002
CE from birth to 5 years of age	96,054	43.93	994	63.72	327	55.71	94,733	43.76	19.96	<0.001	11.95	<0.001	8.01	<0.001

[1] The C1-36* subset included index children with ≥ 36 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 20. C1-36*[1] Index Child Parent Characteristics - Index Child w/ ASD vs. No ASD[2]

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Mother											
Yes – 1 mother identified	n	198,508	1,409	523	196,576						
	%	90.79	90.32	89.10	90.80	-0.48	0.516	-1.70	0.155	1.22	0.400
Yes – multiple potential mothers	n	15,115	122	54	14,939						
	%	6.91	7.82	9.20	6.90	0.92	0.153	2.30	0.028	-1.38	0.299
Mother not identified	n	5,024	29	10	4,985						
	%	2.30	1.86	1.70	2.30	-0.44	0.244	-0.60	0.334	0.16	0.810
Age of mother at infant date of birth[3]	valid N	198,508	1,409	523	196,576						
	mean	32.64	33.36	33.21	32.63	0.73	<0.001	0.57	0.008	0.16	0.517
	SD	4.62	4.70	4.95	4.62						
	median	32.71	33.49	33.44	32.70						
	min	18.00	19.89	20.96	18.00						
	max	49.94	49.53	49.90	49.94						
<20	n	362	1	0	361						
	%	0.18	0.07	0.00	0.18	-0.11	0.324	-0.18	0.327	0.07	0.542
20-29	n	55,735	331	131	55,273						
	%	28.08	23.49	25.05	28.12	-4.63	<0.001	-3.07	0.119	-1.56	0.476
30-34	n	81,056	549	202	80,305						
	%	40.83	38.96	38.62	40.85	-1.89	0.151	-2.23	0.300	0.34	0.891
35-39	n	50,771	418	146	50,207						
	%	25.58	29.67	27.92	25.54	4.13	<0.001	2.38	0.214	1.75	0.452
40-49	n	10,584	110	44	10,430						
	%	5.33	7.81	8.41	5.31	2.50	<0.001	3.11	0.002	-0.61	0.662

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Age of eldest mother at infant date of birth[4]	valid N	213,623	1,531	577	211,515						
	mean	32.80	33.54	33.43	32.79	0.75	<0.001	0.64	0.001	0.11	0.652
	SD	4.74	4.82	4.98	4.74						
	median	32.82	33.68	33.53	32.81						
	min	18.00	19.89	20.96	18.00						
	max	49.99	49.62	49.90	49.99						
Age of youngest mother at infant date of birth[4]	valid N	213,623	1,531	577	211,515						
	mean	32.31	32.97	32.72	32.31	0.66	<0.001	0.41	0.061	0.25	0.311
	SD	4.92	5.03	5.25	4.91						
	median	32.50	33.20	32.99	32.49						
	min	18.00	18.04	18.04	18.00						
	max	49.94	49.53	49.90	49.94						
Father											
Yes – 1 father identified	n	197,064	1,391	529	195,144						
	%	90.13	89.17	90.12	90.14	-0.97	0.201	-0.02	0.989	-0.95	0.522
Yes – multiple potential fathers	n	10,002	93	33	9,876						
	%	4.57	5.96	5.62	4.56	1.40	0.008	1.06	0.219	0.34	0.765
Father not identified	n	11,581	76	25	11,480						
	%	5.30	4.87	4.26	5.30	-0.43	0.449	-1.04	0.260	0.61	0.550

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Age of father at infant date of birth[3]	valid N	197,064	1,391	529	195,144						
	mean	34.74	35.73	35.21	34.73	1.00	<0.001	0.48	0.035	0.52	0.052
	SD	5.17	5.31	5.22	5.16						
	median	34.56	35.65	35.18	34.55						
	min	18.00	18.78	20.10	18.00						
	max	50.00	49.25	49.53	50.00						
<20	n	270	2	0	268						
	%	0.14	0.14	0.00	0.14	0.01	0.948	-0.14	0.394	0.14	0.383
20-29	n	34,724	204	84	34,436						
	%	17.62	14.67	15.88	17.65	-2.98	0.004	-1.77	0.287	-1.21	0.506
30-34	n	70,523	427	173	69,923						
	%	35.79	30.70	32.70	35.83	-5.13	<0.001	-3.13	0.134	-2.01	0.397
35-39	n	61,168	459	178	60,531						
	%	31.04	33.00	33.65	31.02	1.98	0.112	2.63	0.192	-0.65	0.787
40-49	n	30,379	299	94	29,986						
	%	15.42	21.50	17.77	15.37	6.13	<0.001	2.40	0.126	3.73	0.071
Age of eldest father at infant date of birth[4]	valid N	207,066	1,484	562	205,020						
	mean	34.86	35.88	35.41	34.86	1.03	<0.001	0.55	0.012	0.48	0.074
	SD	5.25	5.39	5.29	5.24						
	median	34.66	35.80	35.30	34.65						
	min	18.00	18.78	20.10	18.00						
	max	50.00	49.53	49.53	50.00						

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Age of youngest father at infant date of birth[4]	valid N	207,066	1,484	562	205,020						
	mean	34.46	35.32	35.01	34.45	0.87	<0.001	0.56	0.014	0.30	0.277
	SD	5.44	5.70	5.48	5.44						
	median	34.41	35.39	35.04	34.40						
	min	18.00	18.16	18.56	18.00						
	max	50.00	49.25	49.53	50.00						

[1] The C1-36* subset included index children with ≥ 36 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

[3] Among those index children with exactly one mother/father identified.

[4] Among those index children with at least one mother/father identified.

Table 21 and Table 22 each present clinical characteristics of the C1-36* index children. The distribution of the modified Childhood Chronic Conditions score among the index children is presented in Table 21. Index children with likely and possible ASD had, on average, higher CCC scores (0.53±0.87 and 0.58±0.96, respectively) than index children without ASD (0.26±0.57; $p<0.001$). A higher proportion of index children in the likely ASD cohort were identified in most CCC categories compared with index children without ASD:

- all neuromuscular comorbid conditions (brain and spinal cord malformations, central nervous system degeneration and disease, infantile cerebral palsy, muscular dystrophies and myopathies, epilepsy and seizure disorders; all $p<0.001$; intellectual disability, p=0,011);
- cardiovascular conditions ($p<0.001$);
- respiratory conditions ($p<0.001$);
- gastrointestinal conditions ($p=0.039$);
- metabolic conditions, including amino acid metabolism, carbohydrate metabolism, storage disorders, other metabolic disorders, diabetes (all $p<0.05$);
- other congenital or genetic defects ($p<0.001$); and
- malignant neoplasms ($p=0.009$).

There were no significant differences in the prevalence of renal, hematologic or immunologic conditions or lipid metabolism between index children with likely ASD and index children without ASD. With the exception of metabolic disorder, results comparing index children with possible ASD to those without ASD were similar to results comparing index children with likely ASD to those without ASD.

Approximately 8% of the index children in the likely and possible ASD cohorts had evidence of seizures compared with 2.4% of index children without ASD (both $p<0.001$), as shown in Table 22. In addition, diagnoses indicating pre-term birth were identified in 14.4% of index children with likely ASD and 15.5% of index children with possible ASD vs. 8.0% of index children without ASD (both $p<0.001$). There were no significant differences between index child with likely ASD and those without ASD with respect to vaccination-associated allergies, although index children with possible ASD were more likely to have experienced vaccination-associated allergies than children without ASD ($p=0.001$; Table 22).

Table 21. Modified Childhood Chronic Conditions Score (0-24 Months of Age) – C1- 36*[1] Index Children w/ ASD vs. No ASD[2]

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	mean	SD	mean	SD	mean	SD	mean	SD						
Childhood Chronic Conditions Score (modified)	0.27	0.57	0.53	0.87	0.58	0.96	0.26	0.57	0.27	<0.001	0.32	<0.001	-0.05	0.248
	n	%	n	%	n	%	n	%						
Neuromuscular	3,496	1.60	120	7.69	52	8.86	3,324	1.54	6.16	<0.001	7.32	<0.001	-1.17	0.375
Brain and spinal cord malformations	2,044	0.93	60	3.85	28	4.77	1,956	0.90	2.94	<0.001	3.87	<0.001	-0.92	0.336
Intellectual disability	18	0.01	1	0.06	1	0.17	16	0.01	0.06	0.011	0.16	<0.001	-0.11	0.472
Central nervous system degeneration and disease	94	0.04	5	0.32	3	0.51	86	0.04	0.28	<0.001	0.47	<0.001	-0.19	0.518
Infantile cerebral palsy	456	0.21	28	1.79	12	2.04	416	0.19	1.60	<0.001	1.85	<0.001	-0.25	0.703
Muscular dystrophies and myopathies	115	0.05	5	0.32	2	0.34	108	0.05	0.27	<0.001	0.29	0.002	-0.02	0.942
Epilepsy and seizure disorders	1,253	0.57	47	3.01	25	4.26	1,181	0.55	2.47	<0.001	3.71	<0.001	-1.25	0.153
Cardiovascular	10,351	4.73	146	9.36	67	11.41	10,138	4.68	4.68	<0.001	6.73	<0.001	-2.05	0.156
Respiratory	28,443	13.01	295	18.91	108	18.40	28,040	12.95	5.96	<0.001	5.45	<0.001	0.51	0.787
Renal	219	0.10	2	0.13	1	0.17	216	0.10	0.03	0.723	0.07	0.589	-0.04	0.816
Gastrointestinal	845	0.39	11	0.71	9	1.53	825	0.38	0.32	0.039	1.15	<0.001	-0.83	0.075
Hematologic or immunologic	1,763	0.81	14	0.90	8	1.36	1,741	0.80	0.09	0.681	0.56	0.130	-0.47	0.340

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Metabolic	4,314	1.97	69	4.42	15	2.56	4,230	1.95	2.47	<0.001	0.60	0.293	1.87	0.047
Amino acid metabolism	1,206	0.55	15	0.96	4	0.68	1,187	0.55	0.41	0.028	0.13	0.663	0.28	0.537
Carbohydrate metabolism	1,402	0.64	23	1.47	5	0.85	1,374	0.63	0.84	<0.001	0.22	0.508	0.62	0.257
Lipid metabolism	383	0.18	3	0.19	0	0.00	380	0.18	0.02	0.875	-0.18	0.310	0.19	0.288
Storage disorders	37	0.02	2	0.13	1	0.17	34	0.02	0.11	<0.001	0.15	0.003	-0.04	0.816
Other metabolic disorders	1,194	0.55	23	1.47	4	0.68	1,167	0.54	0.94	<0.001	0.14	0.638	0.79	0.142
Diabetes	259	0.12	5	0.32	1	0.17	253	0.12	0.20	0.020	0.05	0.705	0.15	0.557
Other congenital or genetic defect	6,485	2.97	141	9.04	64	10.90	6,280	2.90	6.14	<0.001	8.00	<0.001	-1.86	0.190
Malignant neoplasms	2,538	1.16	29	1.86	18	3.07	2,491	1.15	0.71	0.009	1.92	<0.001	-1.21	0.088

[1] The C1-36* subset included index children with ≥ 36 months of continuous enrollment (CE) and at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 22. Clinical Characteristics - Seizures, Allergies and Pre-term Birth – C1-36*[1] Index Children w/ ASD vs. No ASD[2]

	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	n	%	n	%	n	%	n	%						
Potential contraindications to vaccination														
Seizures[3]	5,449	2.49	120	7.69	48	8.18	5,281	2.44	5.25	<0.001	5.74	<0.001	-0.48	0.709
Vaccination-associated allergies[3]	999	0.46	10	0.64	8	1.36	981	0.45	0.19	0.272	0.91	0.001	-0.72	0.102
Other potential reasons for vaccination delay or avoidance														
Pre-term birth[3]	17,538	8.02	225	14.42	91	15.50	17,222	7.95	6.47	<0.001	7.55	<0.001	-1.08	0.529

[1] The C1-36* subset included index children with ≥ 36 months of continuous enrollment (CE) and at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

[3] Seizures and vaccine-related allergies presented in this table were measured using each index child's enrollment period from birth to 24 months and preterm birth was measured using each index child's entire enrollment period from birth to disenrollment.

3. Vaccinations and Vaccine-related Infectious Disease Episodes

Table 23 and Table 24 present the associations between index child ASD status and vaccination completion by age (Table 23); vaccine-related infectious diseases (Table 24).

In general, compliance with MMR vaccination was fairly high, as shown in Table 23: 83% of index children had completed at least one MMR vaccination by 24 months of age, 86% by 36 months, 87% by 48 months, and 90% by 60 months of age. There were no statistically significant differences between the proportions of index children with likely ASD or possible ASD and index children without ASD that completed the MMR vaccination at each time point.

The rates of completion of both Hib and PCV vaccinations were higher than were the completion rates for RV (Table 23). At 8 months of age, 71.4% of index children had completed the primary Hib vaccination series; however, just 62.9% of index children had received the final dose in the series by 24 months of age. By 60 months of age, the proportion of index children with a complete Hib vaccination series reached 71.6%. The proportion of index children with PCV vaccination series completion also increased with children's age. Nearly 63% of index children had received the first three doses of the PCV vaccination series at 8 months and 64.3% of index children had received the fourth dose in the series by 24 months, with PCV vaccination completion rates reaching 69.9% by 60 months.

In contrast, Table 23 also shows that overall RV (and subsequently the composite Hib/PCV/RV) vaccination rates were relatively low because RV vaccine was not approved until 2006, therefore only a portion of the sample had the opportunity to receive the RV vaccine at all. The RV vaccination completion rate was approximately 25% by 8 months of age and, in contrast to other vaccines, remained relatively stable despite older age cutoffs. This is not surprising given the maximum age limit for administration of RV vaccine is 8 months (and 0 days) of age, therefore we would expect very few RV vaccinations to be received past the 8-month cutoff (unlike the other vaccines being studied, for which catch-up vaccinations are recommended). The composite Hib/PCV/RV vaccination completion rate was somewhat lower than the RV vaccination completion rate, but followed the same general pattern as the other vaccine measures.

Consistently and significantly higher proportions of index children without ASD completed the RV (and the composite of Hib/PCV/RV) vaccination series compared to children with likely ASD ($p<0.001$ at all time-points). For example, the differences in the RV (and the composite Hib/PCV/RV) vaccination rates between the index children with likely ASD and those without ASD was approximately four percentage points. Rates of completion of the RV (and the composite of Hib/PCV/RV) vaccination series among index children with possible ASD were in-between rates of completion for index children with likely ASD and those without ASD, but were not statistically significantly different than the completion rates in either group.

The descriptive analysis of vaccine-related infectious diseases by index child ASD status is presented in Table 24. Otitis media was, by far, the most prevalent infection among those we measured (Table 24). Eighty-four percent (84%) of index children had at least one otitis media episode; and this percentage differed significantly when comparing index children with likely and possible ASD to index children without ASD (90.6% and 89.4%, respectively vs. 83.9%; both $p<0.001$). Index children in the likely and possible ASD cohorts each had 5.0±4.3 episodes of otitis media, on average, compared with 3.6±3.4 otitis media episodes among index children without

ASD (both p<0.001). In addition, index children with likely ASD had their first otitis media episodes later, on average, than did index children without ASD (14.6±13.5 months vs. 13.6±12.4 months, respectively; p=0.005), however, time to first otitis media episode was not statistically significantly different between index children with possible ASD and those without ASD.

As shown in Table 24, 22.0% of index children with likely ASD, and 24.7% of index children with possible ASD had at least one pneumonia episode (0.33±0.77 and 0.46±1.43 pneumonia episodes on average, respectively), compared with 18.4% of index children without ASD (0.26±0.74 pneumonia episodes on average; all p<0.001). The mean time to the first pneumonia episode was not statistically significantly different between index children with and without ASD.

Meningitis was rare among index children; less than 1% of index children were identified with a meningitis episode. There were no statistically significant differences in the proportions of index children with any meningitis episodes, the average numbers of episodes, or the average time to the first meningitis episode between index children with likely or possible ASD and index children without ASD.

Finally, a higher proportion of index children with likely or possible ASD had at least one episode of gastroenteritis (24.7%and 21.6%, respectively vs. 16.7% among index children without ASD; p<0.01). Index children with likely or possible ASD also had more gastroenteritis episodes, on average (0.36±0.77 and 0.31±0.72, respectively compared to 0.22±0.56 among index children without ASD, p<0.01). As was the case with otitis media, index children with likely ASD had their first episode of gastroenteritis later relative to index children without ASD: 27.1±23.0 months vs. 21.8±18.2 months on average (p<0.001), however, time to first gastroenteritis episode was not statistically significantly different between index children with possible ASD and those without ASD.

A greater proportion of index children with likely ASD had at least one measles/mumps/rubella infection compared with children without ASD; the prevalence of these diseases, however, were very low—much lower than 1%—and the differences between the likely ASD and no ASD cohorts, while statistically significant, were small and not clinically meaningful.

Table 23. C1-36*[1] Index Child Vaccination Completion – Index Child w/ ASD vs. No ASD[2]

Age-appropriate Vaccine Series Completion	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	n	%	n	%	n	%	n	%						
Completion by 8 months of age														
2/3 Hib	156,054	71.37	1,122	71.92	416	70.87	154,516	71.37	0.55	0.630	-0.50	0.789	1.05	0.629
3 PCV	137,467	62.87	979	62.76	351	59.80	136,137	62.88	-0.12	0.919	-3.09	0.122	2.96	0.208
2/3 RV	54,453	24.90	323	20.71	136	23.17	53,994	24.94	-4.23	<0.001	-1.77	0.322	-2.46	0.215
Composite 2/3 Hib + 3 PCV + 2/3 RV	46,577	21.30	275	17.63	113	19.25	46,189	21.33	-3.71	<0.001	-2.08	0.218	-1.62	0.384
Completion by 24 months of age														
3/4 Hib	137,527	62.90	983	63.01	384	65.42	136,160	62.89	0.12	0.921	2.53	0.206	-2.40	0.302
4 PCV	140,619	64.31	985	63.14	370	63.03	139,264	64.33	-1.18	0.331	-1.29	0.514	0.11	0.963
2/3 RV	55,307	25.30	327	20.96	138	23.51	54,842	25.33	-4.37	<0.001	-1.82	0.311	-2.55	0.201
Composite 3/4 Hib + 4 PCV + 2/3 RV	36,098	16.51	199	12.76	93	15.84	35,806	16.54	-3.78	<0.001	-0.70	0.651	-3.09	0.063
MMR	181,837	83.16	1,279	81.99	492	83.82	180,066	83.17	-1.18	0.213	0.64	0.677	-1.83	0.320
Completion by 36 months of age														
3/4 Hib	149,786	68.51	1,062	68.08	421	71.72	148,303	68.50	-0.42	0.720	3.22	0.093	-3.64	0.104
4 PCV	148,848	68.08	1,049	67.24	394	67.12	147,405	68.09	-0.84	0.477	-0.96	0.617	0.12	0.957
2/3 RV	55,315	25.30	327	20.96	138	23.51	54,850	25.33	-4.37	<0.001	-1.83	0.310	-2.55	0.201
Composite 3/4 Hib + 4 PCV + 2/3 RV	42,318	19.35	237	15.19	111	18.91	41,970	19.39	-4.19	<0.001	-0.48	0.771	-3.72	0.037
MMR	188,415	86.17	1,322	84.74	516	87.90	186,577	86.18	-1.44	0.102	1.73	0.226	-3.16	0.063

Age-appropriate Vaccine Series Completion	Total (N=218,647)		(1) Index Child w/ Likely ASD (N=1,560)		(2) Index Child w/ Possible ASD (N=587)		(3) Index Child w/out ASD (N=216,500)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Completion by 48 months of age														
3/4 Hib	155,046	70.91	1,106	70.90	427	72.74	153,513	70.91	-0.01	0.994	1.84	0.328	-1.85	0.399
4 PCV	151,337	69.22	1,065	68.27	401	68.31	149,871	69.22	-0.96	0.415	-0.91	0.633	-0.04	0.984
2/3 RV	55,315	25.30	327	20.96	138	23.51	54,850	25.33	-4.37	<0.001	-1.83	0.310	-2.55	0.201
Composite 3/4 Hib + 4 PCV + 2/3 RV	45,414	20.77	261	16.73	114	19.42	45,039	20.80	-4.07	<0.001	-1.38	0.410	-2.69	0.143
MMR	190,550	87.15	1,342	86.03	522	88.93	188,686	87.15	-1.13	0.185	1.77	0.200	-2.90	0.077
Completion by 60 months of age														
3/4 Hib	156,561	71.60	1,112	71.28	433	73.76	155,016	71.60	-0.32	0.781	2.16	0.246	-2.48	0.254
4 PCV	152,821	69.89	1,077	69.04	408	69.51	151,336	69.90	-0.86	0.459	-0.40	0.835	-0.47	0.834
2/3 RV	55,317	25.30	327	20.96	138	23.51	54,852	25.34	-4.37	<0.001	-1.83	0.310	-2.55	0.201
Composite 3/4 Hib + 4 PCV + 2/3 RV	46,117	21.09	267	17.12	116	19.76	45,734	21.12	-4.01	<0.001	-1.36	0.419	-2.65	0.153
MMR	196,408	89.83	1,402	89.87	537	91.48	194,469	89.82	0.05	0.950	1.66	0.184	-1.61	0.261

[1] The C1—36* subset included index children with ≥ 36 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Likely ASD – index children with 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 24. C1-36*[1] Index Child Vaccination-Associated Infectious Disease Episodes – Index Child w/ ASD vs. No ASD[2]

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Otitis media	valid N	218,647	1,560	587	216,500						
	n	183,608	1,413	525	181,670						
	%	83.97	90.58	89.44	83.91	6.66	<0.001	5.53	<0.001	1.14	0.427
Number of otitis media episodes	valid N	218,647	1,560	587	216,500						
	mean	3.62	4.96	4.83	3.60	1.36	<0.001	1.23	<0.001	0.13	0.541
	SD	3.37	4.25	4.28	3.36						
Proportion of inpatient otitis media episodes among index children with at least one otitis media episode	valid N	183,608	1,413	525	181,670						
	mean	0.00	0.01	0.01	0.00	0.00	0.018	0.00	0.152	0.00	0.651
	SD	0.04	0.05	0.04	0.04						
Time to first otitis media episode (days)	valid N	183,608	1,413	525	181,670						
	mean	408.61	439.06	407.83	408.38	30.68	0.005	-0.55	0.973	31.23	0.108
	SD	370.91	404.70	370.22	370.63						
Pneumonia	valid N	218,647	1,560	587	216,500						
	n	40,364	343	145	39,876						
	%	18.46	21.99	24.70	18.42	3.57	<0.001	6.28	<0.001	-2.71	0.181
Number of pneumonia episodes	valid N	218,647	1,560	587	216,500						
	mean	0.26	0.33	0.46	0.26	0.07	<0.001	0.20	<0.001	-0.13	0.040
	SD	0.74	0.77	1.43	0.74						
Proportion of inpatient pneumonia episodes among index children with at least one pneumonia episode	valid N	40,364	343	145	39,876						
	mean	0.09	0.13	0.19	0.09	0.04	0.013	0.10	<0.001	-0.06	0.063
	SD	0.27	0.30	0.34	0.27						

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Time to first pneumonia episode (days)	valid N	40,364	343	145	39,876						
	mean	884.85	906.35	921.35	884.53	21.82	0.579	36.82	0.586	-15.00	0.840
	SD	651.61	725.33	811.63	650.30						
Meningitis	valid N	218,647	1,560	587	216,500						
	n	627	5	2	620						
	%	0.29	0.32	0.34	0.29	0.03	0.802	0.05	0.806	-0.02	0.942
Number of meningitis episodes	valid N	218,647	1,560	587	216,500						
	mean	0.00	0.00	0.01	0.00	-0.00	0.951	0.00	0.634	-0.00	0.640
	SD	0.07	0.06	0.09	0.07						
Proportion of inpatient meningitis episodes among index children with at least one meningitis episode	valid N	627	5	2	620						
	mean	0.58	0.60	0.25	0.58	0.02	0.931	-0.33	0.333	0.35	0.453
	SD	0.48	0.55	0.35	0.48						
Time to first meningitis episode (days)	valid N	627	5	2	620						
	mean	275.89	585.20	640.00	272.23	312.97	0.190	367.77	0.329	-54.80	0.935
	SD	532.88	725.33	905.10	530.31						
Gastroenteritis	valid N	218,647	1,560	587	216,500						
	n	36,644	385	127	36,132						
	%	16.76	24.68	21.64	16.69	7.99	<0.001	4.95	0.001	3.04	0.140
Number of gastroenteritis episodes	valid N	218,647	1,560	587	216,500						
	mean	0.22	0.36	0.31	0.22	0.14	<0.001	0.09	0.003	0.05	0.163
	SD	0.56	0.77	0.72	0.56						

		Total (N=218,647)	(1) Index Child w/ Likely ASD (N=1,560)	(2) Index Child w/ Possible ASD (N=587)	(3) Index Child w/out ASD (N=216,500)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Proportion of inpatient gastroenteritis episodes among index children with at least one gastroenteritis episode	valid N	36,644	385	127	36,132						
	mean	0.05	0.06	0.06	0.05	0.02	0.196	0.02	0.296	-0.00	0.877
	SD	0.20	0.23	0.22	0.20						
Time to first gastroenteritis episode (days)	valid N	36,644	385	127	36,132						
	mean	656.98	812.02	716.60	655.12	156.90	<0.001	61.48	0.273	95.42	0.169
	SD	547.13	691.46	628.69	544.85						
Measles, mumps or rubella	valid N	218,647	1,560	587	216,500						
	N	661	12	1	648						
	%	0.30	0.77	0.17	0.30	0.47	<0.001	-0.13	0.568	0.60	0.111

[1] The C1-36 subset included index children with ≥ 36 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

4. Association between MMR Vaccination and MMR

Before fitting the regression models for the measles/mumps/rubella (MMR) outcome, we first compared unadjusted rates of MMR outcomes in the C1-36* sample by MMR vaccination status. Table 25 provides the number of records, exposure time in days, number of MMR outcome events, and the rate of MMR infections per person-year (365 days) of observation stratified by vaccinated and unvaccinated exposure time for all index children. The number of records represents the construction of the data set that we used to estimate the MMR Cox proportional hazard regression models, with one observation per index child per MMR vaccination over their observations period. The MMR vaccine is recommended for administration between 12 and 15 months of age, therefore we excluded all time at risk prior to each index child's first birthday as the lack of vaccinations prior to age one precluded our ability to examine the association between MMR vaccination and the MMR outcome. We also excluded children who were identified with an MMR event before their first birthday, because this model did not allow for recurrent events, and therefore these children were not considered at risk for the outcome. The unadjusted rate of MMR outcomes during the unvaccinated exposure time was 0.001 per person-year compared to 0.0003 per person-year during the vaccinated exposure time.

Table 25. C1-36*[1] Measles, Mumps or Rubella Event Summary

MMR Vaccination Level	# Records = 424,930 # Index Children = 218,394			
	# records	# MMR events	exposure time (days)	rate per person-year
No MMR vaccine doses	219,875	141	52,821,153	0.0010
Any (≥1) MMR vaccine dose[2]	205,055	267	288,286,867	0.0003

[1]N=218,394 index children; exposure time captured after year 1 birthday; N=253 index children had MMR event prior to year 1 birthday and were excluded from this analysis.
[2]MMR vaccination captured after year 1 birthday.

The results of the Cox proportional hazard regressions of MMR infection with primary predictors of MMR vaccination status (unvaccinated vs. vaccinated [ref]) and index child ASD status are displayed in Table 26. Three separate Cox proportional hazard regressions were conducted using different sets of covariates: MMR vaccination status as the only independent variable ("unadjusted" result), adjusted for birth year, and adjusted for birth year and index child ASD status. For these models, repeat events were not allowed, therefore once a child experienced an MMR infection, they were considered "immune" to subsequent infections. All models inherently adjusted for age (i.e., time), and a time by vaccination status interaction term was evaluated for each model to determine if the proportionality assumption held.

MMR vaccination was not statistically significantly associated with MMR infection in any of the models. In addition, the time by vaccination status interaction was not statistically significant in any of these models, indicating that the hazard ratios were constant across time (age), and therefore this term was not included in the final models. MMR events were quite rare (only 661 in the entire data set – see Table 27) making effect estimates very imprecise. Finally, the association between MMR vaccination status and MMR infection was not found to be confounded by the index child's ASD status.

In the model adjusted for index child ASD status, the independent effect of ASD status on MMR events was positive and statistically significant. Children with possible or likely ASD had almost twice the probability of infection with MMR compared with children without ASD ($p<0.001$). However, this estimate, though statistically significant, is very imprecise due to the very low rate of MMR infections. Only 12 index children with likely ASD were identified with an MMR infection; of these 12, just 2 were unvaccinated.

Table 26. C1-36*[1] Relative Risk of Measles, Mumps or Rubella[2] by MMR Vaccination Level

Primary Predictors	Outcome: Measles, Mumps, or Rubella Infection (First Event Only)			
	hazard ratio (relative risk)	lower 95% CI	upper 95% CI	p-value
Unadjusted[3]				
MMR vaccination status - unvaccinated[4] (ref: any MMR vaccination)	1.033	0.828	1.287	0.776
Adjusted for birth year				
MMR vaccination status - unvaccinated (ref: any MMR vaccination)	0.991	0.795	1.236	0.939
Adjusted for birth year and index child ASD status				
MMR vaccination status - unvaccinated (ref: any MMR vaccination)	0.992	0.795	1.237	0.942
Likely/possible ASD (ref: no ASD)[5]	2.894	1.632	5.132	<0.001

[1] N=218,394 index children; exposure captured after year 1 birthday; N=253 index children had an MMR event prior to year 1 birthday and were excluded from this analysis.

[2] N=408 total events across all index children.

[3] Because time is synonymous with age, all models inherently adjust for age, therefore, even "unadjusted" results provide age-adjusted estimates.

[4] MMR vaccination captured after year 1 birthday.

[5] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; No ASD – index children with 0 ASD diagnoses.

Full model results are provided in Appendix A, Table 3.

5. Association between RV Vaccination and Gastroenteritis

Table 27 displays the descriptive, unadjusted gastroenteritis event summary. Like the MMR event summary presented in Table 25, the gastroenteritis event summary provides the number of discrete records from the data set that we built for the gastroenteritis Cox proportional hazards model, as well as the number of gastroenteritis events, exposure time, and resulting rate of gastroenteritis events per person-year (365 days). In this case, because repeat gastroenteritis events were allowed, the number of records represents one observation per index child per RV vaccination or gastroenteritis event over their observations period. The rates of gastroenteritis events per person-year were similar between index children with no rotavirus (RV) vaccination doses and those with at least one dose: 0.0417 vs. 0.0409, respectively.

Table 27. C1-36*[1] Gastroenteritis Event Summary

RV Vaccination Level	# Records = 315,246 # Index Children = 106,240			
	# records	# gastroenteritis events	exposure time (days)	rate per person-year
No RV vaccine doses	116,259	8,247	72,268,469	0.0417
Any (≥1) RV vaccine dose	198,987	11,446	102,158,745	0.0409

[1]N=106,240 index children born during or after 2006.

Table 28 presents a summary of the gastroenteritis Cox proportional hazards models. An unadjusted model was fit, controlling only for RV vaccination status (no RV vaccination doses vs. any RV vaccination dose) by gastroenteritis event (first event [Event 1], any subsequent event [Event 2+]). The probability of a first gastroenteritis event was 15.3% higher among unvaccinated index children relative to index children with at least one RV vaccination dose in the unadjusted model. This relationship remained positive and statistically significant after we adjusted for index child and parent demographic/sociodemographic characteristics and clinical characteristics that may affect the likelihood of vaccination. The probability of a first gastroenteritis event was 7.1% higher in children with no RV vaccination doses in both the fully adjusted model and the fully adjusted model with index child ASD status included. The association between RV vaccination status and subsequent (2+) gastroenteritis events was not significant. Finally, index child ASD status did not confound the relationships between RV vaccination and gastroenteritis events. However, index child likely or possible ASD status was associated with a 27.1% higher rate of gastroenteritis infection compared to no ASD.

Table 28. C1-36*[1] Relative Risk of Gastroenteritis[2] by RV Vaccination Level - Events 1 and 2+

Primary Predictors	Outcome: Gastroenteritis (Event 1, Any Subsequent Event [Event 2+])			
	hazard ratio (relative risk)	lower 95% CI	upper 95% CI	p-value
Unadjusted[3]				
Event 1 - No rotavirus vaccination doses (ref: any RV vaccination)	1.153	1.116	1.192	<0.001
Events 2+ - No rotavirus vaccination doses (ref: any RV vaccination)	1.023	0.952	1.100	0.531
Fully adjusted[4] without index child ASD status				
Event 1 - No rotavirus vaccination doses (ref: any RV vaccination)	1.071	1.033	1.109	<0.001
Events 2+ - No rotavirus vaccination doses (ref: any RV vaccination)	0.956	0.888	1.029	0.229
Fully adjusted with index child ASD status				
Event 1 - No rotavirus vaccination doses (ref: any RV vaccination)	1.071	1.033	1.110	<0.001
Events 2+ - No rotavirus vaccination doses (ref: any RV vaccination)	0.957	0.889	1.030	0.244
Likely/possible ASD (ref: no ASD)[5]	1.271	1.112	1.453	<0.001

[1] N=106,240 index children born during or after 2006.
[2] N=19,693 gastroenteritis events.
[3] Because time is synonymous with age, all models inherently adjust for age, therefore, even "unadjusted" results provide age-adjusted estimates.
[4] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, seizure, allergies, pre-term birth.
[5] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; No ASD – index children with 0 ASD diagnoses.
Full model results are provided in Appendix A, Table 4.

6. Association between Hib and PCV Vaccinations and Otitis Media, Pneumonia, and Meningitis

The results of the analyses examining the associations between Hib and PCV vaccination status and otitis media, pneumonia, and meningitis are displayed in Table 29 through Table 32. Table 29 shows the descriptive unadjusted rates of otitis media, pneumonia, and meningitis *per index child* by Hib and PCV vaccination status. The prevalence of otitis media and pneumonia and, less consistently, meningitis, appears to be inversely associated with vaccination status in our sample. That is, the unadjusted prevalence of these infectious diseases was higher for partially vaccinated index children relative to unvaccinated children; the unadjusted prevalence of otitis media was also higher among fully vaccinated children than among partially vaccinated index children.

Table 29. C1-36* Bacterial Infection Event Summary - Cumulative Incidence Rates from Birth to 36 Months Stratified by Vaccination Status at 36 Months

	# index children (N=218,647)	Otitis Media		Pneumonia		Meningitis	
		# events	rate/ index child	# events	rate/ index child	# events	rate/ index child
Hib vaccination completion at 36 months							
Unvaccinated[1]	14,545	20,091	1.3813	1634	0.1123	38	0.0026
Partially vaccinated[2]	54,316	140,883	2.5938	9509	0.1751	171	0.0031
Fully vaccinated[3]	149,786	429,361	2.8665	24648	0.1646	445	0.0030
PCV vaccination completion at 36 months							
Unvaccinated[1]	18,384	28,585	1.5549	2195	0.1194	42	0.0023
Partially vaccinated[2]	51,415	137,640	2.6770	9166	0.1783	169	0.0033
Fully vaccinated[3]	148,848	424,110	2.8493	24430	0.1641	443	0.0030

[1] Unvaccinated = 0 doses by 36 months.
[2] Partially vaccinated = at least one dose but not complete vaccination series at 36 months.
[3] Fully vaccinated = completed dose series by 36 months.

Results aggregated at the bacterial infection level are included in Appendix A, Table 2.

a. Otitis media

Table 30 presents the results of the otitis media models: unadjusted, fully adjusted, and fully adjusted with index child ASD status included. The results from the Cox proportional hazard regressions (which adjust for the age of the index child) correspond with the descriptive unadjusted rates shown in Table 29. Partially vaccinated and unvaccinated time was associated with lower probabilities of otitis media events relative to fully vaccinated time. All vaccination status hazard ratios were significant at $p<0.001$.

- No Hib vaccinations relative to a completed Hib vaccination series was associated with a 33% lower probability of otitis media in the unadjusted model and a 32% lower probability of otitis media in the fully adjusted models (with and without index child ASD status).

- Partial Hib vaccination relative to a completed Hib vaccination series was associated with a 5% lower probability of otitis media in the unadjusted model, and an approximately 2.5% lower probability of otitis media in the fully adjusted models.
- No PCV vaccinations relative to a completed PCV vaccination series was associated with a 20% lower probability of otitis media in the unadjusted model and a 23% lower probability of otitis media in both fully adjusted models (including and not including index child ASD status).
- Partial PCV vaccination relative to a completed PCV vaccination series was associated with a 2% lower probability of otitis media in the unadjusted model and a 4.6% lower probability of otitis media in both of the fully adjusted models.

ASD status was not a significant confounder of the relationship between vaccination status and otitis media infection. ASD status was associated with a significantly higher probability of otitis media; index children with likely or possible ASD had a 19.7% higher probability of otitis media compared with index children without ASD.

Table 30. C1-36*[1] Relative Risk of Otitis Media[2] by HIB/PCV Vaccination Level

Primary Predictors	Outcome: Otitis Media Event			
	hazard ratio (relative risk)	lower 95% CI	upper 95% CI	p-value
Unadjusted[3]				
HIB vaccination status (ref: fully vaccinated[4])				
Unvaccinated[5]	0.666	0.648	0.684	<0.001
Partially vaccinated[6]	0.951	0.942	0.960	<0.001
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.799	0.780	0.817	<0.001
Partially vaccinated	0.979	0.970	0.989	<0.001
Fully adjusted[7] without index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	0.680	0.662	0.698	<0.001
Partially vaccinated	0.974	0.965	0.984	<0.001
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.773	0.756	0.791	<0.001
Partially vaccinated	0.954	0.945	0.963	<0.001
Fully adjusted with index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	0.680	0.662	0.698	<0.001
Partially vaccinated	0.975	0.965	0.984	<0.001
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.773	0.756	0.791	<0.001
Partially vaccinated	0.954	0.945	0.963	<0.001
Likely/possible ASD (ref: no ASD)[8]	1.197	1.153	1.241	<0.001

[1] N=218,647 index children.
[2] N=790,767 otitis media events.
[3] Because time is synonymous with age, all models inherently adjust for age, therefore, even "unadjusted" results provide age-adjusted estimates.
[4] Fully vaccinated = completed series.

[5] Unvaccinated = 0 doses.
[6] Partially vaccinated = at least one dose but series not complete.
[7] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, seizure (time-varying), vaccine-related allergies (time-varying), pre-term birth.
[8] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; No ASD – index children with 0 ASD diagnoses.

Full model results are provided in Appendix A, Table 5.

b. Pneumonia

The results of the pneumonia models are in Table 31. The Cox proportional hazard regression results (which adjust for the age of the index child) reflect the unadjusted descriptive rates of pneumonia displayed in Table 29. Unvaccinated status tended to be associated with a significantly lower probability of pneumonia infection compared to fully vaccinated status. The hazard ratios for partial vaccination compared with full vaccination were not always statistically significant; when the hazard ratios associated with partial vaccination status were statistically significant, however, they suggested a protective effect of partial vaccination relative to full vaccination.

- No Hib vaccinations relative to a completed Hib vaccination series was associated with a 16% lower probability of pneumonia in both the unadjusted model and both adjusted models. The hazard ratios for partial Hib vaccination compared to complete Hib vaccination were not statistically significant in any of the models.
- No PCV vaccinations relative to a completed PCV vaccination series was associated with a 13% lower probability of pneumonia in the unadjusted model and in both adjusted models.
- Partial PCV vaccination relative to a completed PCV vaccination series was associated with a 4% lower probability of pneumonia in the unadjusted model and a 6% lower probability of pneumonia in each of the fully adjusted models.

The relationship between Hib and PCV vaccination status and pneumonia was not confounded by ASD. In addition, no statistically significant association between ASD and pneumonia was observed.

Table 31. C1-36*[1] Relative Risk of Pneumonia[2] by HIB/PCV Vaccination Level

Primary Predictors	Outcome: Pneumonia Event			
Unadjusted[3]				
HIB vaccination status (ref: fully vaccinated[4])				
Unvaccinated[5]	0.836	0.763	0.916	<0.001
Partially vaccinated[6]	1.024	0.992	1.056	0.141
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.871	0.793	0.956	0.004
Partially vaccinated	0.955	0.926	0.984	0.003

Primary Predictors	Outcome: Pneumonia Event			
Fully adjusted[7] without index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	0.841	0.768	0.921	<0.001
Partially vaccinated	1.014	0.983	1.047	0.383
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.872	0.794	0.958	0.004
Partially vaccinated	0.944	0.914	0.975	<0.001
Fully adjusted with index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	0.841	0.768	0.921	<0.001
Partially vaccinated	1.014	0.983	1.047	0.382
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.872	0.794	0.958	0.004
Partially vaccinated	0.944	0.914	0.975	<0.001
Likely/possible ASD (ref: no ASD)[8]	1.013	0.903	1.138	0.822

[1] N=218,647 index children.
[2] N=56,178 pneumonia events.
[3] Because time is synonymous with age, all models inherently adjust for age, therefore, even "unadjusted" results provide age-adjusted estimates.
[4] Fully vaccinated = completed dose series.
[5] Unvaccinated = 0 doses.
[6] Partially vaccinated = at least one dose but not complete.
[7] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, seizure (time-varying), vaccine-related allergies (time-varying), pre-term birth.
[8] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; No ASD – index children with 0 ASD diagnoses.

Full model results are provided in Appendix A, Table 6.

c. Meningitis

Table 32 shows the results of the meningitis models, which were modeled with similar specifications as those for otitis media and pneumonia. The unadjusted descriptive rates of meningitis (Table 29) did not appear to vary strongly by vaccination status. The rate of meningitis did appear to be slightly lower among unvaccinated index children compared with partially and fully vaccinated index children, but those differences were not as pronounced as the differences observed for otitis media and pneumonia. The results of the Cox proportional hazard regressions for meningitis (which adjust for the age of the index child) are different than the unadjusted descriptive rates of meningitis by vaccination level. In the regression models, there were no statistically significant associations observed between Hib or PCV vaccination status and meningitis.

There was an association observed between ASD status and meningitis. Index children with likely or possible ASD had a 57% lower probability of meningitis compared with index children without ASD. Due to the small number of meningitis events, this effect was not strongly significant, with a wide confidence interval and p=0.037.

Table 32. C1-36*[1] Relative Risk of Meningitis[2] by HIB/PCV Vaccination Level

Primary Predictors	Outcome: Meningitis Event			
	hazard ratio (relative risk)	lower 95% CI	upper 95% CI	p-value
Unadjusted[3]				
HIB vaccination status (ref: fully vaccinated[4])				
Unvaccinated[5]	1.641	0.547	4.918	0.377
Partially vaccinated[6]	1.307	0.807	2.117	0.276
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.962	0.380	2.432	0.935
Partially vaccinated	0.915	0.568	1.474	0.715
Fully adjusted[7] without index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	1.685	0.594	4.780	0.326
Partially vaccinated	1.392	0.854	2.269	0.185
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.774	0.317	1.889	0.573
Partially vaccinated	0.778	0.478	1.268	0.314
Fully adjusted with index child ASD status				
HIB vaccination status (ref: fully vaccinated)				
Unvaccinated	1.687	0.594	4.792	0.326
Partially vaccinated	1.390	0.853	2.266	0.186
PCV vaccination status (ref: fully vaccinated)				
Unvaccinated	0.772	0.316	1.886	0.570
Partially vaccinated	0.779	0.478	1.268	0.315
Likely/possible ASD (ref: no ASD)[8]	0.427	0.192	0.950	0.037

[1] N=218,647 index children.
[2] N=721 meningitis events.
[3] Because time is synonymous with age, all models inherently adjust for age, therefore, even "unadjusted" results provide age-adjusted estimates.
[4] Fully vaccinated = completed dose series.
[5] Unvaccinated = 0 doses.
[6] Partially vaccinated = at least one dose but not complete b.
[7] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, seizure (time-varying), vaccine-related allergies (time-varying), pre-term birth.
[8] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; No ASD – index children with 0 ASD diagnoses.

Full model results are provided in Appendix A, Table 7.

E. Discussion

1. Summary of Findings

In our results, rotavirus vaccination was significantly associated with reduced gastroenteritis risk. However, our results did not provide evidence of lower risk of other vaccine-related infectious

disease outcomes associated with MMR, PCV or Hib vaccinations. Instead we observed increases in otitis media and pneumonia episodes associated with complete Hib and PCV vaccination series relative to partial series or no vaccinations. These results may initially appear inconsistent with *a priori* expectation, but when outcome specificity and the potential for medical surveillance bias are considered, this pattern of findings appears less surprising. We will comment further on this below.

a. Common Infectious Outcomes

Rotavirus

The rotavirus vaccine appears protective against gastroenteritis as vaccination is associated with a 7.1% decrease in the risk of an initial infection. No statistically significant association between vaccination and gastroenteritis was found for subsequent infections. And although a child's ASD status did not confound the relationship between rotavirus vaccination status and gastroenteritis infections, ASD was associated with an increased risk of gastroenteritis infections (HR=1.27; 95% CI=1.11-1.45).

The detected increased risk of 7.1% associated with a lack of rotavirus vaccination may appear modest, but the definition of the gastroenteritis outcome in these claims data is broad and undoubtedly includes many non-rotavirus gastroenteritis cases in addition to rotavirus cases. While rotavirus vaccination has demonstrated some protection against gastrointestinal symptoms caused by other organisms,[41] the presence of non-rotavirus gastroenteritis in our outcome definition introduces misclassification which likely pushes the effect toward the null.

Moreover, there may also be some misclassification of unvaccinated children in our data set. We know that claims data are not comprehensive in their representation of vaccination receipt. The National Immunization Survey consistently reports rates of vaccination that are somewhat higher than we observed in our sample, as presented in Report 1, supporting the idea that claims data may miss vaccinations administered in certain settings such as schools, public health clinics, etc. Thus, some of the children in our study who appear unvaccinated may have received vaccinations in settings that were not included in their claims data; such misclassification would also bias our results against showing a protective effect.

Otitis Media and Pneumonia

Our results suggest that Hib or PCV vaccines are associated with an *increased* risk of otitis media and pneumonia episodes. After adjusting for age using Cox proportional hazard regression models, children were 32% more likely to have an otitis media infection and 16% more likely to have pneumonia *with a complete* Hib vaccination series compared to being unvaccinated. Similarly, children were 23% more likely to have an otitis media infection and 13% more likely to have pneumonia with a complete PPV vaccination series relative to being unvaccinated.

As was the case with the gastroenteritis outcome, the otitis media and pneumonia outcomes are both non-specific; in fact, in the age ranges of the children's follow up in this study, the fever and respiratory symptoms consistent with otitis media and pneumonia cases have predominantly viral causes that would be unaffected by vaccination. Additionally, a diagnosis for otitis media can be coded on an acute care visit for fever or ear pain, even when a child may not be confirmed with otitis media or prescribed an antibiotic. Rule out coding like this may also occur for pneumonia, but perhaps to a lesser extent because the need for care is justified by the severity of

the symptoms rather than by the diagnosis of a condition for which a prescription is needed. While the inclusion of episodes that are not truly vaccine-preventable otitis media and pneumonia in our outcome definition would move the effect estimate toward the null, it would not be expected to make vaccination appear to increase the risk of these outcomes. However, the attenuation of the protective effect caused by outcome misclassification would also make our resulting effect estimates more vulnerable to other biases. In particular, there could be medical surveillance bias, where families who miss appointments for vaccinations, intentionally or otherwise, may also be less likely to seek care for milder symptoms such as earache, fever or upper respiratory symptoms. There could also be bias due to unmeasured confounding, for example, families that actively avoid vaccination —many of which are required for daycare—may be the same families who are not exposing their children to groups of other children such as those in daycare settings.

Similar to findings for gastroenteritis, children with ASD also appeared to have higher rates of otitis media infection (HR=1.20; 95% CI=1.15-1.24) but not pneumonia. However, a child's ASD status did not appear to confound the relationship between Hib or PCV vaccination status and otitis media or pneumonia. It is possible that the observed association between ASD and otitis media and pneumonia could also be in part attributable to medical surveillance bias because a child with a chronic condition such as ASD likely has more frequent contact with the health care system and more opportunities to be diagnosed with a condition for symptoms that are mild.

There are some additional steps that could be taken in future analyses to potentially reduce the impact of outcome misclassification and medical surveillance bias. First, these data could be re-analyzed restricting outcomes to those with more specific definitions and/or validated by clinical, pharmacy, or laboratory information. To attempt to control for medical surveillance bias, data could be reanalyzed incorporating adjustment for variables believed to be associated with propensity to seek care, such as the number of observed preventive health care visits or visits overall. An analysis could also be attempted using an instrumental variable for vaccination status (such as provider-level vaccination tendency indicators) with instrumental variable analysis approaches used to re-estimate the association between individual vaccination status and the outcomes (done by simultaneously estimating the instrument's effect on both vaccination and infectious disease outcomes). The instrumental variable approach is unlikely a panacea, however, as the available instruments are probably fairly weak and there are some challenges to using instrumental variable approaches with time-varying data.

b. Rare infectious disease outcomes

Measles, Mumps, Rubella

MMR vaccination was ***not*** significantly associated with MMR infections (HR=0.99; 95% CI= 0.80-1.24) – however, this was likely related in part to the rarity of these outcomes and the resulting statistical imprecision. Also adding to the difficulty of detecting a significant individual-level vaccine protective effect is the importance of group-level herd immunity, which was not considered in this analysis (e.g., by including variables capturing local community MMR vaccine coverage rates).

While children with likely ASD did have an increased risk of MMR infection—independent of vaccination status—this was based on only 12 diagnoses total (out of the 408 cases of measles,

mumps, or rubella that occurred after 12 months of age) among children with ASD; of these 12, just 2 were in children who were unvaccinated.

Meningitis

Neither Hib nor PCV vaccination status were significantly associated with the occurrence of meningitis, but meningitis was rare in our sample (721 infections), resulting in non-significant hazard ratios with wide confidence intervals. In fact, the point estimates for the association between Hib and PCV vaccination and meningitis events did suggest that meningitis rates were lower in subjects receiving Hib (by 64%) than in those not receiving the vaccine - although this effect was not statistically significant as there were only 38 meningitis events during the unvaccinated time at risk. The diagnosis of meningitis is more specific than that of otitis media and pneumonia and would, as a result, be less frequently misclassified than these other outcomes. On the other hand, viral meningitis is now more common than bacterial (largely as a result of vaccines) though early in the illness it is difficult to distinguish between the two, meaning meningitis can still be misclassified by mistaking viral meningitis for bacterial or vaccine-related. The severity of the condition and its symptoms almost always warrants medical intervention, which would also make the outcome less susceptible to surveillance bias than the other endpoints.

Children with ASD actually appeared *less* likely to have meningitis (HR=0.43; 95% CI=0.19-0.95), suggesting that some of the results we have previously seen associating ASD with increased risk of infectious diseases could indeed be driven by surveillance bias. Alternatively, the lower risk we see might indicate that meningitis is harder to diagnose in children with ASD as its hallmark features, stiff neck and headache in the presence of fever, require the patient to report the symptoms that raise the diagnostic possibility of meningitis.

V. ASD and Other Neuropsychiatric Health Outcomes

A. Background

In 1998, Andrew Wakefield and colleagues published a research study that implicated the measles-mumps-rubella (MMR) vaccine as a possible cause of autism.[42] This study, intended to examine a potential link between measles virus and bowel disease, included twelve children who, after a period of normal development, regressed developmentally as well as displayed gastrointestinal symptoms. In eight of the children, parents or physicians retrospectively associated the behavioral symptoms with the receipt of the MMR vaccine. Afterwards, reports by parents as well as a few studies with serious methodological flaws continued to link MMR vaccine receipt with autism, particularly regressive autism.[16] Subsequently, more general concerns arose that the upward trends of MMR vaccination and autism diagnoses were related, despite the MMR vaccine having been introduced in 1971 and the trend of increasing autism diagnoses not appearing until the late eighties.[16]

The results of the Wakefield study have not been confirmed or replicated in other studies.[5,6,7,8,9,10,11,12,13] Most of its original authors have disavowed its results and a retraction/apology was subsequently published.[43,44] In 2005, and updated in 2012, the Cochrane Library systematically reviewed studies of both the safety and effectiveness of MMR vaccine. All total, 5 RCTs and over 50 other studies (of varying study design and quality) were reviewed, including more than 14 million children, and no credible evidence of an association between the MMR vaccine and any long-term disability was found.[11]

However, parents continue to worry about the safety of the vaccine and its potential link to autism despite the views of the scientific community;[45, 46, 47, 48, 49] indeed, concerns about vaccines in general and MMR in particular may have even increased.[49,50,51] These concerns have, in turn, led to lower vaccination levels as they are a leading reason cited by parents when deferring or refusing vaccines, particularly MMR.[52]

Lower vaccination levels have the potential to threaten public health by reducing both individual and herd immunity, resulting in outbreaks of vaccine-preventable conditions. Despite a declaration that measles had been eliminated in the United States as of 2000,[53] there have been several large outbreaks in recent years, with the majority of cases occurring in the unvaccinated.[31] Should herd immunity become affected, the reemergence of vaccine-preventable diseases could reduce some of the public health gains provided by vaccines and result in increases in morbidity and mortality.

Speculation about a link between vaccines and autism remains a significant individual and public policy issue, chiefly because ASD often results in profound disability, and its etiology is poorly understood. Furthermore, because ASD itself is so heterogeneous in presentation, previous research has not ruled out the possibility that vaccines contribute to autism in a small subgroup or subset of individuals or under particular circumstances.[16] Of particular interest is whether there is a genetic vulnerability to ASD in some individuals. If that were the case, the association between MMR vaccination and ASD might differ among families that have another child with ASD and families that have no children with ASD. Therefore, this second component of the study uses our large sample of younger siblings with enrollment from birth until five years of age to examine any association between MMR vaccination and ASD taking into account older sibling ASD status.

B. Research Questions and Causal Diagram

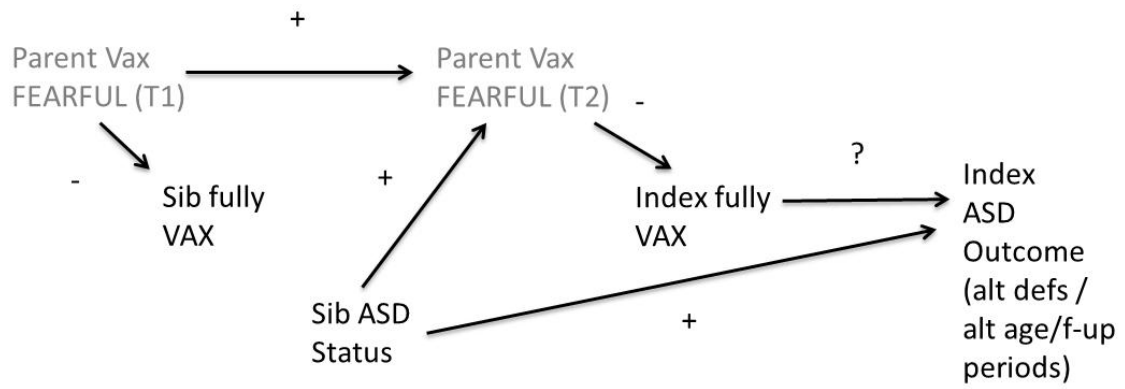
There are three distinct research questions related to examining the recurrence rate of ASD among siblings and the potential association between the receipt of the MMR vaccine and ASD among the younger siblings of children with and without ASD.

1. What is the recurrence rate of ASD—i.e., among the index children who have an older sibling with ASD, what is the rate of ASD among the younger siblings?
2. What is the association between index child MMR vaccination status and index child ASD status?
3. Does older sibling ASD status modify the relationship between index child MMR vaccination status and index child ASD status?

In addition to measuring ASD as an outcome in index children, we assessed a set of diverse neuropsychiatric outcomes as they related to MMR vaccination status. These outcomes were chosen as potential early and broad (sensitive vs. specific) markers for ASD. The chief reason for assessing these additional outcomes was to allow additional sensitivity analysis in the case of inadequate numbers of ASD cases.

Figure 4 presents the causal diagram for the association of ASD and MMR vaccination status (questions #2 and 3).

Figure 4. Causal Diagram for ASD and MMR Relationship



The figure above shows the analytic framework for the analyses addressing the question of whether vaccination status is associated with ASD outcome. The hypothesized relationships between parent attitudes, older sibling ASD status, and index child vaccination status are as they were in the causal diagram for the earlier analysis examining infectious disease outcomes and their relationship to vaccination status. Although the preponderance of evidence to date does not support an association between vaccination status and ASD risk, as shown in the diagram, it could be argued that older sibling ASD status, as it relates to parent vaccination attitudes, could be a negative confounder of this association. In other words, accepting that older sibling ASD status is positively associated with index child ASD risk (as is well-supported by recurrence risk studies),[14,15] parents who have older children with ASD are more vaccine fearful and thus less likely to fully vaccinate subsequent children, these subsequent children who are at higher risk for ASD by virtue of family history would be over-represented in the under-immunized population.

Therefore, the ASD risk in the unvaccinated group would be artifactually inflated and contrasts between fully vaccinated versus under-vaccinated children would be biased toward the null. Because the prevalence of having an older sibling with ASD is low, it is unlikely that this confounding would be strong, but our dataset will allow for adjustment for older sibling ASD status when estimating MMR vaccine-ASD associations and can provide data on the magnitude of this potential confounder.

In addition, some have expressed concerns that an effect of vaccination on increased ASD risk could be limited to a susceptible subgroup. While it is unclear what the important susceptibility factors might be, we can, in these analyses, explore a group already at higher risk of ASD by virtue of having an older sibling with ASD. To do this we estimated the associations between index child MMR vaccination status and ASD risk separately in index children with older siblings with and without ASD.

C. Analytic Approach

1. Descriptive Analysis

This analysis was performed on the C1-60* subgroup. As with the previous analysis of vaccinations and infectious disease outcomes, all variables used to respond to this research question were analyzed descriptively with counts and percentages for dichotomous and categorical variables, and means, standard deviations, medians, and ranges for continuous measures. Variables were stratified by index child ASD status, as they were for the previous analysis.

In addition, index child ASD and neuropsychiatric outcomes were stratified and compared between older siblings with and without likely ASD and by index child MMR vaccination status (yes/no).

2. Multivariable Regression Analysis

The multivariable analyses examined the associations between MMR vaccination status, older sibling ASD status, and index child ASD status (likely, possible or no ASD). All regressions were estimated among index children meeting the inclusion criteria who were continuously enrolled from birth through at least 60 months of age (C1-60* subgroup; n = 96,054). Separate models were constructed defining the outcome as likely ASD and also as likely or possible ASD.

The multivariable analyses were conducted using Cox proportional hazard regression models, with index child ASD diagnosis as the outcome, and MMR vaccination as a time-varying covariate. MMR vaccination was parameterized as 0, 1 or 2 doses (in contrast to the MMR infection outcome models which parameterized MMR vaccination as vaccinated or unvaccinated). Multiple events were not a factor in this analysis; therefore we did not need to employ the PWP extension of the traditional Cox proportional hazards model used in the previous section.

In addition, we included an interaction between MMR vaccination status and age (time). We report the time-specific hazard ratios below for the models in which the time by vaccination status interaction was statistically significant.

Each index child was observed for ASD outcome for a variable period of *at least* 60 months, from birth through the end of follow-up. Cox proportional hazards models allow the risk of detecting ASD to change at different ages (essentially adjusting for age) but assume that the ratio of the

hazards across different MMR vaccine exposure groups are constant at different ages (i.e., across time). Because this assumption of proportionality of hazards is restrictive, we estimated all of the models with interaction terms between age (i.e., time) and MMR vaccination status which relaxes the proportionality assumption. These interaction terms allowed us to explore whether the hazard ratios comparing risk of ASD across different levels of MMR vaccination (0, 1 or 2) changed at different ages. These interactions were all statistically significant and we believe the pattern of age-specific MMR effect estimates was meaningful in interpreting results. Consequently, we report age-specific MMR vaccination effects in the results below. Specifically, we present estimates of the effect on ASD risk of one MMR dose compared to no MMR exposure as well as the effect of two MMR doses compared to no MMR exposure, with age-specific MMR effects over the plausible age ranges for MMR exposure – age 1 to 5 for the first MMR dose and age 4-5 for the second MMR exposure dose.

We present results from unadjusted models, as well as fully adjusted models that adjust for multiple covariates. For each model, additional covariates were finalized based on clinical rationale, descriptive analysis results, and statistical significance.

The covariates included in the fully adjusted model include birth year, gender, US Census region, race/ethnicity, maternal/paternal highest level of education, mother's age at index child's birth, father's age at index child's birth, index child's continuous enrollment with mental health benefits, Childhood Chronic Condition Score (modified) measured from birth through 24 months of age, the presence of seizures or allergies to vaccines between birth and the end of follow-up (included as time-varying covariates), and evidence of pre-term birth. The covariates were not evaluated for proportionality as these covariates served as adjustment variables rather than primary predictors.

We also wanted to explore the possibility that older sibling ASD status confounded or modified the relationship between index child MMR vaccination status and the risk of ASD. To do this we included an interaction term between MMR vaccination status and older sibling ASD status in addition to the interaction between age and MMR vaccination status. This results in the generation of separate age-specific MMR hazard ratios for index children with and without older siblings with ASD.

D. Results

1. Patient Characteristics

Table 33 displays demographic characteristics for the C1-60* sample. Index children in the C1-60* sample were born between 2001 and 2007 in order to allow for a minimum of 5 years of follow-up time for all children in the sample.

Fifty-one percent (51%) of the sample was male and, as was the case in the C1-36* sample and expected from previous literature about the high proportion of males among children with ASD, there was a large difference in the proportion of males among index children with likely ASD (80.9%) and with possible ASD (72.8%) relative to index children without ASD (50.8%; both $p<0.001$). A higher proportion of index children with likely and possible ASD (14.8% and 15.3%, respectively) vs. index children without ASD were from the Northeast region (11.0%; both

p<0.05). There were no other statistically significant differences between the index child with likely ASD and index child without ASD cohorts by geographic region.

Seventy-three percent (73%) of the C1-60* sample was White. A slightly larger proportion of index children without ASD were African-American/Black: 3.8% compared with 2.3% of index children with likely ASD (p=0.017). There were no statistically significant differences in the distribution of other race categories between index children with likely or possible ASD and those without ASD. With the exception of a slightly smaller proportion of index children with possible ASD in the $75,000-$99,999 household income category (18.0%) relative to index children without ASD (22.7%; p=0.047), there were no statistically significant differences in household income categories between cohorts.

The proportion of index children with likely ASD with parents whose highest level of education was a high school diploma (21.4%) was significantly lower than among the corresponding proportion of children without ASD (24.6%; p=0.020). Conversely, the prevalence of at least one parent with an associate degree was higher among children with likely ASD (12.7%) compared with 9.6% of children without ASD; p=0.001).

As shown in Table 34, index children with likely ASD in the C1-60* sample had longer periods of continuous enrollment, on average, compared with index children without ASD or those with possible ASD. Index children with likely ASD were enrolled in their commercial health plans for 7.5±1.8 years, on average, compared to index child without ASD cohort who were enrolled 7.1±1.7 years (p<0.001) and those with possible ASD who were enrolled an average of 7.2±1.8 years (p=0.019).

Index children's parent characteristics are provided in Table 35. Almost 91% of index children had exactly one mother identified by the family identification algorithm (Table 1); 7.1% of index children had more than one potential mother identified. Among index children with just one mother identified in the database, the mother's average age was 32.8±4.6 years; and this differed significantly between index children with likely or possible ASD and index children without ASD (33.3±4.8 years and 33.5±5.1 years, respectively vs. 32.8±4.6 years; both p<0.05). As with the C1-36* sample, we computed the average age of all mothers (including the multiple mothers associated with one index child), using the oldest mother's age and the youngest mother's age to provide a range of average mothers' ages. These results were similar to the mother's average age among index children with only one mother identified; the average age of the oldest potential mothers was 33.0±4.7, and the average age of the youngest potential mothers was 32.5±4.9. In the multivariable analysis, mother's age was categorized: <20, 20-29, 30-34, 35-39, 40-49, multiple (mothers), and no mother identified.

The age of the index child's father was handled in a similar manner. Overall, 90.9% of index children had exactly one father identified in the database by the family identification algorithm (Table 1), and approximately 4.6% of index children had more than one father identified. Among index children with just one father identified, the father's average age was 34.9±5.1 years; and this differed significantly between index children in the likely ASD cohort compared to those without ASD (35.7±5.1 years vs. 34.9±5.1 years, respectively; p<0.001). Estimates for the father's average age including index children with more than one potential father were similar to the father's average age among index children with only one father identified; the average age of the oldest

potential fathers was 35.0±5.2, and the average age of the youngest potential fathers was 34.6±5.4. In the multivariable analysis, father's age was categorized in the same way as mother's age.

Table 36 provides the descriptive analyses of older sibling characteristics by index child ASD status. Overall, 2.0% of index children had an older sibling with ASD, on average; and this differed significantly between index children in the likely and possible ASD cohorts compared with those without ASD (13.5% and 10.7%, respectively vs. 1.9%; both $p<0.001$). The proportions of index children with likely and possible ASD who had 2+ older siblings with ASD were also statistically significantly higher than corresponding proportions among index children without ASD (all $p<0.001$), although the actual proportions and the differences between them were very small.

Table 37 provides additional detail about the relationship between index children and their older sibling(s) with ASD. Index children with at least one older sibling with ASD were 2.6±2.4 years old on average at first evidence of ASD in their older sibling(s), and on average, older siblings with ASD were 4.6±3.1 years old at the time of the index child's birth. Index children with likely ASD more often had a female older sibling with ASD; 24.6% of index children with likely ASD had an older female sibling with ASD compared with 16.6% of index children without ASD ($p=0.017$).

Table 33. C1-60*[1] Index Child Demographic Characteristics - Index Child w/ ASD vs. No ASD[2]

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	n	%	n	%	n	%	n	%						
Birth year														
2001	11,529	12.00	113	11.37	49	14.98	11,367	12.00	-0.63	0.543	2.99	0.097	-3.62	0.084
2002	11,789	12.27	141	14.19	35	10.70	11,613	12.26	1.93	0.066	-1.56	0.392	3.48	0.108
2003	12,475	12.99	157	15.79	42	12.84	12,276	12.96	2.84	0.008	-0.11	0.951	2.95	0.196
2004	12,879	13.41	147	14.79	39	11.93	12,693	13.40	1.39	0.201	-1.47	0.435	2.86	0.197
2005	14,495	15.09	137	13.78	49	14.98	14,309	15.10	-1.32	0.247	-0.12	0.952	-1.20	0.588
2006	15,725	16.37	138	13.88	60	18.35	15,527	16.39	-2.51	0.034	1.96	0.340	-4.47	0.050
2007	17,162	17.87	161	16.20	53	16.21	16,948	17.89	-1.69	0.166	-1.68	0.428	-0.01	0.996
2008	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
2009	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
2010	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
2011	0	0.00	0	0.00	0	0.00	0	0.00	–	–	–	–	–	–
Gender														
Male	49,130	51.15	804	80.89	238	72.78	48,088	50.76	30.12	<0.001	22.02	<0.001	8.10	0.002
Female	46,924	48.85	190	19.11	89	27.22	46,645	49.24	-30.12	<0.001	-22.02	<0.001	-8.10	0.002
Geographic region														
Northeast	10,610	11.05	147	14.79	50	15.29	10,413	10.99	3.80	<0.001	4.30	0.013	-0.50	0.825
Midwest	28,170	29.33	299	30.08	85	25.99	27,786	29.33	0.75	0.606	-3.34	0.186	4.09	0.158
South	40,611	42.28	396	39.84	142	43.43	40,073	42.30	-2.46	0.118	1.12	0.681	-3.59	0.252
West	16,631	17.31	152	15.29	50	15.29	16,429	17.34	-2.05	0.089	-2.05	0.328	0.00	1.000
Other	32	0.03	0	0.00	0	0.00	32	0.03	-0.03	0.562	-0.03	0.740	–	–

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Race/Ethnicity														
White	70,257	73.14	736	74.04	224	68.50	69,297	73.15	0.89	0.527	-4.65	0.058	5.54	0.051
African-American/ Black	3,591	3.74	23	2.31	14	4.28	3,554	3.75	-1.44	0.017	0.53	0.615	-1.97	0.061
Native Hawaiian or Pacific Islander	82	0.09	0	0.00	1	0.31	81	0.09	-0.09	0.356	0.22	0.176	-0.31	0.081
American Indian or Alaskan Native	192	0.20	1	0.10	1	0.31	190	0.20	-0.10	0.482	0.11	0.671	-0.21	0.408
Asian	3,325	3.46	37	3.72	11	3.36	3,277	3.46	0.26	0.652	-0.10	0.925	0.36	0.764
Hispanic	8,768	9.13	91	9.15	34	10.40	8,643	9.12	0.03	0.973	1.27	0.425	-1.24	0.505
Other	1,647	1.71	22	2.21	5	1.53	1,620	1.71	0.50	0.224	-0.18	0.801	0.68	0.448
Unknown	7,598	7.91	77	7.75	35	10.70	7,486	7.90	-0.16	0.856	2.80	0.061	-2.96	0.096
No SES information	594	0.62	7	0.70	2	0.61	585	0.62	0.09	0.729	-0.01	0.989	0.09	0.860
Household income														
Under $50,000	13,300	13.85	118	11.87	47	14.37	13,135	13.87	-1.99	0.070	0.51	0.791	-2.50	0.235
$50,000 - $74,999	21,903	22.80	213	21.43	79	24.16	21,611	22.81	-1.38	0.301	1.35	0.562	-2.73	0.302
$75,000 - $99,999	21,741	22.63	226	22.74	59	18.04	21,456	22.65	0.09	0.948	-4.61	0.047	4.69	0.073
$100,000 - $124,999	16,058	16.72	189	19.01	60	18.35	15,809	16.69	2.33	0.051	1.66	0.421	0.67	0.790
$125,000+	12,292	12.80	133	13.38	45	13.76	12,114	12.79	0.59	0.578	0.97	0.599	-0.38	0.861
Unknown	10,166	10.58	108	10.87	35	10.70	10,023	10.58	0.28	0.771	0.12	0.942	0.16	0.935
No SES information	594	0.62	7	0.70	2	0.61	585	0.62	0.09	0.729	-0.01	0.989	0.09	0.860

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Maternal/paternal education														
Less than 12th Grade	962	1.00	9	0.91	6	1.83	947	1.00	-0.09	0.766	0.84	0.130	-0.93	0.169
High School Diploma	23,608	24.58	213	21.43	75	22.94	23,320	24.62	-3.19	0.020	-1.68	0.481	-1.51	0.567
Some college/ Associate Degree	46,784	48.70	515	51.81	158	48.32	46,111	48.67	3.14	0.049	-0.36	0.898	3.49	0.273
Bachelor Degree or higher	23,114	24.06	245	24.65	86	26.30	22,783	24.05	0.60	0.661	2.25	0.342	-1.65	0.550
Unknown	1,293	1.35	11	1.11	2	0.61	1,280	1.35	-0.24	0.506	-0.74	0.247	0.50	0.432
No SES information	214	0.22	1	0.10	0	0.00	213	0.22	-0.12	0.409	-0.22	0.391	0.10	0.566
No mothers/fathers identified	79	0.08	0	0.00	0	0.00	79	0.08	-0.08	0.362	-0.08	0.601	–	–

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 34. C1-60*[1] Index Child Enrollment Characteristics - Index Child w/ ASD vs. No ASD[2]

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	mean	SD	mean	SD	mean	SD	Mean	SD						
Length of continuous enrollment (CE) (years)	7.06	1.70	7.45	1.80	7.18	1.84	7.06	1.70	0.40	<0.001	0.12	0.223	0.27	0.019

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status is classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 35. C1-60*[1] Index Child Parent Characteristics - Index Child w/ ASD vs. No ASD[2]

		Total (N=96,054)	(1) Index Child w/ Likely ASD (N=994)	(2) Index Child w/ Possible ASD (N=327)	(3) Index Child w/out ASD (N=94,733)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Mother											
Yes – 1 mother identified	n	87,373	891	295	86,187						
	%	90.96	89.64	90.21	90.98	-1.34	0.142	-0.76	0.630	-0.58	0.765
Yes – multiple potential mothers	n	6,843	89	26	6,728						
	%	7.12	8.95	7.95	7.10	1.85	0.024	0.85	0.551	1.00	0.577
No mother identified	n	1,838	14	6	1,818						
	%	1.91	1.41	1.83	1.92	-0.51	0.242	-0.08	0.912	-0.43	0.584
Age of mother at infant date of birth[3] (years)	valid N	87,373	891	295	86,187						
	mean	32.81	33.30	33.46	32.80	0.50	0.001	0.66	0.028	-0.16	0.622
	SD	4.57	4.75	5.10	4.57						
	median	32.91	33.48	33.56	32.90						
	min	18.03	19.89	20.96	18.03						
	max	49.90	48.10	49.90	49.87						
<20	n	150	1	0	149						
	%	0.17	0.11	0.00	0.17	-0.06	0.664	-0.17	0.475	0.11	0.565
20-29	n	23,166	213	72	22,881						
	%	26.51	23.91	24.41	26.55	-2.64	0.075	-2.14	0.406	-0.50	0.861
30-34	n	36,007	352	107	35,548						
	%	41.21	39.51	36.27	41.25	-1.74	0.294	-4.97	0.083	3.23	0.323
35-39	n	23,219	254	85	22,880						
	%	26.57	28.51	28.81	26.55	1.96	0.187	2.27	0.379	-0.31	0.920
40-49	n	4,831	71	31	4,729						
	%	5.53	7.97	10.51	5.49	2.48	0.001	5.02	<0.001	-2.54	0.177

		Total (N=96,054)	(1) Index Child w/ Likely ASD (N=994)	(2) Index Child w/ Possible ASD (N=327)	(3) Index Child w/out ASD (N=94,733)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Age of eldest mother at infant date of birth[4] (years)	valid N	94,216	980	321	92,915						
	mean	32.95	33.51	33.57	32.94	0.57	<0.001	0.63	0.027	-0.06	0.840
	SD	4.69	4.90	5.07	4.68						
	median	33.02	33.69	33.72	33.01						
	min	18.03	19.89	20.96	18.03						
	max	49.97	49.62	49.90	49.97						
Age of youngest mother at infant date of birth[4] (years)	valid N	94,216	980	321	92,915						
	mean	32.47	32.86	33.05	32.46	0.40	0.016	0.59	0.046	-0.19	0.557
	SD	4.88	5.12	5.28	4.87						
	median	32.70	33.17	33.12	32.70						
	min	18.00	18.04	18.79	18.00						
	max	49.90	48.10	49.90	49.87						
Father											
Yes – 1 father identified	n	87,266	890	299	86,077						
	%	90.85	89.54	91.44	90.86	-1.33	0.149	0.57	0.719	-1.90	0.320
Yes – multiple potential fathers	n	4,432	59	14	4,359						
	%	4.61	5.94	4.28	4.60	1.33	0.046	-0.32	0.783	1.65	0.256
No father identified	n	4,356	45	14	4,297						
	%	4.53	4.53	4.28	4.54	-0.01	0.989	-0.25	0.825	0.25	0.852
Age of father at infant date of birth[3] (years)	valid N	87,266	890	299	86,077						
	mean	34.89	35.69	35.11	34.88	0.81	<0.001	0.23	0.443	0.58	0.094
	SD	5.11	5.13	5.45	5.11						
	median	34.72	35.70	34.90	34.71						
	min	18.00	19.70	20.10	18.00						
	max	50.00	49.25	49.11	50.00						
<20	n	270	2	0	268						
	%	0.14	0.14	0.00	0.14	0.01	0.948	-0.14	0.394	0.14	0.383
20-29	n	34,724	204	84	34,436						
	%	17.62	14.67	15.88	17.65	-2.98	0.004	-1.77	0.287	-1.21	0.506

		Total (N=96,054)	(1) Index Child w/ Likely ASD (N=994)	(2) Index Child w/ Possible ASD (N=327)	(3) Index Child w/out ASD (N=94,733)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
30-34	n	70,523	427	173	69,923						
	%	35.79	30.70	32.70	35.83	-5.13	<0.001	-3.13	0.134	-2.01	0.397
35-39	n	61,168	459	178	60,531						
	%	31.04	33.00	33.65	31.02	1.98	0.112	2.63	0.192	-0.65	0.787
40-49	n	30,379	299	94	29,986						
	%	15.42	21.50	17.77	15.37	6.13	<0.001	2.40	0.126	3.73	0.071
Age of eldest father at infant date of birth[4] (years)	valid N	91,698	949	313	90,436						
	mean	35.01	35.82	35.30	35.00	0.82	<0.001	0.30	0.306	0.52	0.133
	SD	5.19	5.22	5.53	5.19						
	median	34.82	35.81	35.04	34.81						
	min	18.00	19.70	20.10	18.00						
	max	50.00	49.25	49.11	50.00						
Age of youngest father at infant date of birth[4] (years)	valid N	91,698	949	313	90,436						
	mean	34.61	35.27	35.01	34.60	0.67	<0.001	0.41	0.183	0.26	0.476
	SD	5.39	5.56	5.73	5.39						
	median	34.57	35.45	34.84	34.56						
	min	18.00	18.16	18.56	18.00						
	max	50.00	49.25	49.11	50.00						

[1] The C1-60* subset included index children with ≥ 60months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

[3] Among those index children with exactly one mother/father identified.

[4] Among those index children with at least one mother/father identified.

Table 36. C1-60*[1] Index Child Sibling ASD Status - Index Children w/ ASD vs. No ASD[2]

Among Older Siblings with at least 6 Months CE		Total (N=96,054)	(1) Index Child w/ Likely ASD (N=994)	(2) Index Child w/ Possible ASD (N=327)	(3) Index Child w/out ASD (N=94,733)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
At least one older sibling with ASD	valid N	96,054	994	327	94,733						
	n	1,964	134	35	1,795						
	%	2.04	13.48	10.70	1.89	11.59	<0.001	8.81	<0.001	2.78	0.192
Number of older siblings with ASD	valid N	96,054	994	327	94,733						
	mean	0.02	0.15	0.12	0.02	0.13	<0.001	0.10	<0.001	0.04	0.147
	SD	0.15	0.42	0.37	0.14						
	median	0.00	0.00	0.00	0.00						
	min	0.00	0.00	0.00	0.00						
	max	6.00	5.00	4.00	6.00						
0	n	94,090	860	292	92,938						
	%	97.96	86.52	89.30	98.11	-11.59	<0.001	-8.81	<0.001	-2.78	0.192
1	n	1,883	121	34	1,728						
	%	1.96	12.17	10.40	1.82	10.35	<0.001	8.57	<0.001	1.78	0.387
2	n	77	11	0	66						
	%	0.08	1.11	0.00	0.07	1.04	<0.001	-0.07	0.633	1.11	0.056
3	n	1	1	0	0						
	%	0.00	0.10	0.00	0.00	0.10	<0.001	–	–	0.10	0.566
4 or more	n	3	1	1	1						
	%	0.00	0.10	0.31	0.00	0.10	<0.001	0.30	<0.001	-0.21	0.408

Table 37. C1-60*[1] Index Child Sibling ASD Characteristics – Index Children w/ ASD vs. No ASD[2]

Index Children with at least One Older Sibling with ASD		Total (N=1,964)	(1) Index Child w/ Likely ASD (N=134)	(2) Index Child w/ Possible ASD (N=35)	(3) Index Child w/out ASD (N=1,795)	(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
At least one male older sibling with ASD	n	1,645	104	29	1,512						
	%	83.76	77.61	82.86	84.23	-6.62	0.045	-1.38	0.825	-5.25	0.500
At least one female older sibling with ASD	n	336	33	6	297						
	%	17.11	24.63	17.14	16.55	8.08	0.017	0.60	0.925	7.48	0.349
Age of index child at first evidence of ASD in an older sibling (if index child is not yet born, age of index child is 0) (years)	valid N	1,964	134	35	1,795						
	mean	2.58	2.07	1.98	2.63	-0.56	0.002	-0.65	0.108	0.10	0.801
	SD	2.35	1.97	2.13	2.38						
	median	2.11	1.67	1.16	2.17						
	min	0.00	0.00	0.00	0.00						
	max	11.31	10.99	7.24	11.31						
Age of oldest sibling with any ASD at index child birth (includes older siblings with possible ASD)	valid N	1,964	134	35	1,795						
	mean	4.62	3.68	4.14	4.70	-1.02	<0.001	-0.57	0.291	-0.46	0.369
	SD	3.11	2.63	2.84	3.14						
	median	3.55	2.66	3.11	3.64						
	min	0.74	0.90	1.13	0.74						
	max	17.91	13.32	11.83	17.91						

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 38 displays the clinical characteristics of the C1-60* index children. The distribution of the modified Childhood Chronic Conditions score among index children is presented in Table 38. Index children with likely and possible ASD had, on average, higher CCC scores (0.50±0.82 and 0.61±1.0, respectively) than did index children without ASD (0.26±0.56; both $p<0.001$). Similar to the comparison in the C1-36* sample, higher proportions of index children with likely and possible ASD, relative to index children without ASD, were identified with many of the conditions in the CCC categories, although there were fewer statistically significant differences between the cohorts in the C1-60* sample:

- all neuromuscular comorbid conditions except intellectual disability among children in the likely ASD cohort (i.e., brain and spinal cord malformations, central nervous system degeneration and disease, infantile cerebral palsy, muscular dystrophies and myopathies, epilepsy and seizure disorders; all $p<0.01$);
- cardiovascular (all $p<0.001$);
- respiratory (all $p<0.001$);
- carbohydrate metabolism ($p=0.015$) and other metabolic disorders ($p<0.001$) among index children with likely ASD; and
- other congenital or genetic defect (all $p<0.001$)
- gastrointestinal ($p<0.001$), hematologic/immunologic conditions ($p=0.026$) and malignant neoplasms ($p=0.002$) among children with possible ASD.

There were no significant differences in the prevalence of renal disorders, amino acid metabolism, storage disorders, lipid metabolism or diabetes between index children with likely or possible ASD and index children without ASD.

Seven percent (7.2%) of index children with likely ASD and 8.3% of index children with possible ASD were identified with seizures compared with 2.4% of index children without ASD (both $p<0.001$), as shown in Table 39. Indications of pre-term birth were identified in 13.4% of index children with likely ASD and 16.2% of index children with possible ASD vs. 7.9% of index children without ASD (both $p<0.001$). Index children with possible ASD were more likely to have experienced vaccine-associated allergies than those without ASD (1.5% vs. 0.4%; $p=0.002$), however there were no statistically significant differences between index children with likely ASD and those without ASD with respect to vaccination-associated allergies.

Table 38. C1-60*[1] Modified Childhood Chronic Conditions Score (0-24 Months of Age) – Index Child w/ ASD vs. No ASD[2]

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	mean	SD	mean	SD	mean	SD	mean	SD						
Childhood Chronic Conditions Score (modified)	0.27	0.57	0.50	0.82	0.61	1.01	0.26	0.56	0.23	<0.001	0.35	<0.001	-0.12	0.061
	n	%	n	%	n	%	n	%						
Neuromuscular	1,528	1.59	72	7.24	33	10.09	1,423	1.50	5.74	<0.001	8.59	<0.001	-2.85	0.099
Brain and spinal cord malformations	881	0.92	32	3.22	17	5.20	832	0.88	2.34	<0.001	4.32	<0.001	-1.98	0.100
Intellectual disability	10	0.01	0	0.00	1	0.31	9	0.01	-0.01	0.759	0.30	<0.001	-0.31	0.081
Central nervous system degeneration and disease	38	0.04	2	0.20	2	0.61	34	0.04	0.17	0.007	0.58	<0.001	-0.41	0.241
Infantile cerebral palsy	209	0.22	16	1.61	10	3.06	183	0.19	1.42	<0.001	2.86	<0.001	-1.45	0.102
Muscular dystrophies and myopathies	44	0.05	3	0.30	2	0.61	39	0.04	0.26	<0.001	0.57	<0.001	-0.31	0.429
Epilepsy and seizure disorders	546	0.57	34	3.42	17	5.20	495	0.52	2.90	<0.001	4.68	<0.001	-1.78	0.148
Cardiovascular	4,418	4.60	81	8.15	35	10.70	4,302	4.54	3.61	<0.001	6.16	<0.001	-2.55	0.157
Respiratory	12,706	13.23	185	18.61	67	20.49	12,454	13.15	5.47	<0.001	7.34	<0.001	-1.88	0.453
Renal	81	0.08	2	0.20	1	0.31	78	0.08	0.12	0.197	0.22	0.162	-0.10	0.730
Gastrointestinal	356	0.37	5	0.50	6	1.83	345	0.36	0.14	0.471	1.47	<0.001	-1.33	0.022
Hematologic or immunologic	736	0.77	10	1.01	6	1.83	720	0.76	0.25	0.375	1.07	0.026	-0.83	0.235

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
Metabolic	1,856	1.93	36	3.62	7	2.14	1,813	1.91	1.71	<0.001	0.23	0.765	1.48	0.190
Amino acid metabolism	552	0.57	7	0.70	0	0.00	545	0.58	0.13	0.593	-0.58	0.169	0.70	0.128
Carbohydrate metabolism	587	0.61	12	1.21	3	0.92	572	0.60	0.60	0.015	0.31	0.465	0.29	0.668
Lipid metabolism	171	0.18	3	0.30	0	0.00	168	0.18	0.12	0.355	-0.18	0.446	0.30	0.320
Storage disorders	16	0.02	0	0.00	0	0.00	16	0.02	-0.02	0.682	-0.02	0.814	–	–
Other metabolic disorders	488	0.51	13	1.31	3	0.92	472	0.50	0.81	<0.001	0.42	0.283	0.39	0.576
Diabetes	115	0.12	3	0.30	1	0.31	111	0.12	0.18	0.093	0.19	0.321	-0.00	0.991
Other congenital or genetic defect	2,830	2.95	87	8.75	35	10.70	2,708	2.86	5.89	<0.001	7.84	<0.001	-1.95	0.291
Malignant neoplasms	1,154	1.20	15	1.51	10	3.06	1,129	1.19	0.32	0.360	1.87	0.002	-1.55	0.075

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 39. C1-60*[1] Clinical Characteristics - Seizures, Allergies and Pre-term Birth – Index Child w/ ASD vs. No ASD[2]

	Total (N=96,054)		(1) Index Child w/ Likely ASD (N=994)		(2) Index Child w/ Possible ASD (N=327)		(3) Index Child w/out ASD (N=94,733)		(1) vs. (3) Difference	(1) vs. (3) p-value	(2) vs. (3) Difference	(2) vs. (3) p-value	(1) vs. (2) Difference	(1) vs. (2) p-value
	n	%	n	%	n	%	n	%						
Potential contraindications to vaccination														
Seizures[3]	2,372	2.47	72	7.24	27	8.26	2,273	2.40	4.84	<0.001	5.86	<0.001	-1.01	0.546
Vaccination-associated allergies[3]	408	0.42	5	0.50	5	1.53	398	0.42	0.08	0.688	1.11	0.002	-1.03	0.063
Other potential reasons for vaccination delay or avoidance														
Pre-term birth[3]	7,660	7.97	133	13.38	53	16.21	7,474	7.89	5.49	<0.001	8.32	<0.001	-2.83	0.202

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child ASD status was classified into three categories: Likely ASD - index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

[3] Seizures and allergies were measured using each index child's enrollment period from birth to 24 months and preterm birth wa measured using each index child's entire enrollment period from birth to disenrollment.

2. ASD and other Neuropsychiatric Outcomes

In order to evaluate the association between older sibling ASD status and subsequent development of ASD or other neuropsychiatric conditions in the index child, ASD and neuropsychiatric condition outcomes were analyzed, stratified by older sibling ASD status as shown in Table 40. Older sibling ASD status was significantly associated with ASD status among index children. Among index children with an older sibling with likely ASD, 6.8% also had likely ASD, and another 1.8% were identified as having possible ASD. In comparison, among index children without any evidence of ASD in an older sibling, just 0.9% had evidence of ASD, and 0.3% were identified as having possible ASD (all $p<0.001$).

Older sibling ASD status was also associated with neuropsychiatric conditions in the index child. A significantly higher proportion of index children who had at least one older sibling with ASD (Table 40) had a diagnosis indicating a neuropsychiatric condition compared with index children without any evidence of ASD among older siblings (26.5% vs. 12.7%; $p<0.001$).

To evaluate the association between index child MMR vaccination status and index child ASD and other neuropsychiatric outcomes, these outcomes are presented descriptively in Table 41 stratified by index child MMR vaccination status. There were no statistically significant differences in index child ASD status by index child MMR vaccination status. There was, however, a statistically significant difference in the proportion of index children identified with neuropsychiatric outcomes by MMR status: 13.1% of children who received at least one MMR vaccination were identified with a neuropsychiatric outcome compared with 12.1% of index children who did not receive an MMR vaccination ($p<0.001$ for a 1.05 percentage-point difference).

Table 40. C1-60*[1] Index Child Neuropsychiatric Health Outcomes - Older Sibling w/ ASD vs. No Older Sibling w/ ASD[2]

ASD and Other Neuropsychiatric Conditions among Index Children		Total (N=96,054)	(1) Older Sibling w/ Likely ASD (N=1,964)	(2) No ASD in an Older Sibling (N=94,090)	(1) vs. (2) Difference	(1) vs. (2) p-value
ASD status[3]						
Likely	n	994	134	860		
	%	1.03	6.82	0.91	-5.91	<0.001
Possible	n	327	35	292		
	%	0.34	1.78	0.31	-1.47	<0.001
Likely or possible	n	1,321	169	1,152		
	%	1.38	8.60	1.22	-7.38	<0.001
None	n	94,733	1,795	92,938		
	%	98.62	91.40	98.78	7.38	<0.001
Neuropsychiatric condition	n	12,450	521	11,929		
	%	12.96	26.53	12.68	-13.85	<0.001

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Older sibling ASD status was determined for all older siblings with ≥ 6 months CE and was classified into two categories: Likely ASD - older siblings with 2+ ASD diagnoses and No ASD – older siblings with 0 ASD diagnoses.

[3] Index child ASD status was classified as follows: Likely ASD – index children with 2+ ASD diagnoses; Possible ASD –index children with only 1 ASD diagnosis; Likely or Possible ASD – index children with 1+ ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

Table 41. C1-60*[1] Index Child Neuropsychiatric Health Outcomes - Index Child MMR Vaccination vs. No MMR Vaccination[2]

		Total (N=96,054)	(1) Index Child MMR Vaccination (N=80,231)	(2) Index Child No MMR Vaccination (N=15,823)	(1) vs. (2) Difference	(1) vs. (2) p-value
ASD status[3]						
Likely	n	994	812	182		
	%	1.03	1.01	1.15	-0.14	0.117
Possible	n	327	273	54		
	%	0.34	0.34	0.34	-0.00	0.984
Likely or possible	n	1,321	1,085	236		
	%	1.38	1.35	1.49	-0.14	0.170
None	n	94,733	79,146	15,587		
	%	98.62	98.65	98.51	0.14	0.170
Neuropsychiatric condition	n	12,450	10,544	1,906		
	%	12.96	13.14	12.05	1.10	<0.001

[1] The C1-60* subset included index children with ≥ 60 months of continuous enrollment (CE) and with at least one older sibling CE ≥ 6 months.

[2] Index child MMR vaccination status was classified as: MMR Vaccination - evidence of MMR vaccination from 12-24 months of age and No MMR Vaccination – no evidence of MMR vaccination from 12-24 months of age.

[3] Index child ASD status was classified was follows: Likely ASD – index children with 2+ ASD diagnoses; Possible ASD – index children with only 1 ASD diagnosis; Likely or Possible ASD – index children with 1+ ASD diagnosis; and No ASD – index children with 0 ASD diagnoses.

3. Association between MMR Vaccination Status and ASD

To examine whether index child MMR vaccination status is associated with having ASD, and to determine if older sibling ASD status confounds or modifies this relationship, we further evaluated the association between index child MMR vaccination and ASD status using Cox proportional hazards regression models.

Table 42 displays the results of the unadjusted ASD model, showing the age-specific effects of one MMR dose by 2, 3, 4 and 5 years, and of two MMR doses by 5 years, without adjusting for any additional covariates or stratifying on older sibling ASD status. In the unadjusted model, MMR vaccination is not associated with an increased risk of ASD for any number of doses at any age. Results were very similar for the "Likely ASD" and "Likely or Possible ASD" outcomes, and adjustment for additional covariates (Table 43) had little effect on these results.

Table 44 presents the results from the fully adjusted model incorporating the additional interaction between MMR vaccination and older sibling ASD status. Consequently, separate age-specific hazard ratio estimates are now displayed for index children with an older sibling with likely ASD (top rows) and without any evidence of ASD among older siblings (bottom rows). Neither one nor two doses of MMR vaccine was associated with a statistically significant increase in ASD risk in either of these two groups at any age.

Several of the multivariable analysis results actually suggest that the ASD risk is lower in children with MMR exposure versus those without MMR exposure. This could be explained by a tendency among parents who have concerns about their child's development early on, to choose to avoid vaccination, which would then artificially increase the risk of ASD detection in the unexposed group at that age. The hazard ratios more strongly suggest lower risk of ASD among MMR-exposed children in families where there is already a child with ASD. This is not unexpected as these families might be more attuned to recognize delays in very young children and/or may more readily be prompted to make a decision to avoid vaccination when they observe delays in their younger child. For the first MMR dose, the hazard ratio estimates which suggest lower risk in those with MMR vaccination also tend to be strongest at younger ages. This is also consistent with this hypothesis because these are the hazard ratios being estimated closest to the time that first dose vaccination decisions are typically being made. At older ages, this trend is weaker since the events occurring at older ages more likely reflect cases where parental concerns about their child's development did not arise until after a decision about the first MMR dose was made.

For the second MMR dose, the hazard ratio estimates around the time when vaccination decisions are being made for dose two (5 years of age) are also suggestive of a protective effect, which supports our hypothesis of vaccine avoidance due to parental concerns about developmental delay. In fact, two doses of MMR vaccine at 5 years of age are associated with a statistically significantly lower risk of likely or possible ASD among index children who have an older sibling with ASD.

Table 42. C1-60*[1] Relative Risk of ASD[2] by Index Child MMR Vaccination Status, Unadjusted with Time Interaction

Time-/Age-Specific Hazard Ratios	Index Child ASD = Likely/Possible				Index Child ASD = Likely			
	hazard ratio	lower 95% CI	upper 95% CI	p-value	hazard ratio	lower 95% CI	upper 95% CI	p-value
One MMR dose at 2 years (731 days)	0.839	0.663	1.062	0.145	0.789	0.606	1.025	0.076
One MMR dose at 3 years (1096 days)	0.871	0.731	1.037	0.120	0.853	0.702	1.037	0.111
One MMR dose at 4 years (1461 days)	0.903	0.751	1.087	0.280	0.924	0.743	1.148	0.475
One MMR dose at 5 years (1827 days)	0.937	0.723	1.214	0.622	1.000	0.732	1.367	1.000
Two MMR doses at 5 years (1827 days)	0.909	0.691	1.197	0.498	0.931	0.667	1.301	0.677

[1] N=96,054 likely/possible/no ASD index children with likely/no older sibling ASD; N=95,727 likely/no ASD index children with likely/no older sibling ASD.

[2] N=1,321 likely/possible/no ASD index children; N=994 likely/no ASD index children.

[3] MMR vaccination doses captured after year 1 birthday.

Table 43. C1-60*[1] Relative Risk of ASD[2] by Index Child MMR Vaccination Status, Fully Adjusted[3] with Time Interaction

Time-/Age-Specific Hazard Ratios	Index Child ASD = Likely/Possible[4]				Index Child ASD = Likely[4]			
	hazard ratio	lower 95% CI	upper 95% CI	p-value	hazard ratio	lower 95% CI	upper 95% CI	p-value
One MMR dose at 2 years (731 days)	0.849	0.671	1.076	0.176	0.793	0.609	1.032	0.084
One MMR dose at 3 years (1096 days)	0.875	0.735	1.042	0.134	0.851	0.700	1.035	0.106
One MMR dose at 4 years (1461 days)	0.901	0.750	1.084	0.270	0.914	0.735	1.136	0.416
One MMR dose at 5 years (1827 days)	0.929	0.717	1.202	0.574	0.981	0.718	1.340	0.904
Two MMR doses at 5 years (1827 days)	0.894	0.680	1.175	0.420	0.916	0.657	1.278	0.607

[1] N=96,054 likely/possible/no ASD index children with likely/no older sibling ASD; N=95,727 likely/no ASD index children with likely/no older sibling ASD.

[2] N=1,321 likely/possible/no ASD index children; N=994 likely/no ASD index children.

[3] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, continuous enrollment with mental health carve-out benefit, Childhood Chronic Conditions Score, seizure, allergies, pre-term birth

[4] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; Likely ASD – index children with 2+ ASD diagnoses; No ASD – index children with 0 ASD diagnoses.

[5] MMR vaccination doses captured after year 1 birthday.

Full model results are provided in Appendix A, Table 8.

Table 44. C1-60*[1] Relative Risk of ASD[2] by Index Child MMR Vaccination Status, Fully Adjusted[3] with Time Interaction, Older Sibling ASD Status, and Older Sibling ASD Status Interacted with MMR Vaccination Status

Time-/Age-Specific Hazard Ratios	Index Child ASD = Likely/Possible[4]				Index Child ASD = Likely[4]			
	hazard ratio	lower 95% CI	upper 95% CI	p-value	hazard ratio	lower 95% CI	upper 95% CI	p-value
Older sibling without ASD								
One MMR dose at 2 years (731 days)	0.975	0.759	1.253	0.845	0.907	0.686	1.200	0.495
One MMR dose at 3 years (1096 days)	0.997	0.820	1.213	0.978	0.967	0.777	1.204	0.764
One MMR dose at 4 years (1461 days)	1.020	0.828	1.256	0.855	1.031	0.807	1.316	0.809
One MMR dose at 5 years (1827 days)	1.043	0.788	1.380	0.771	1.099	0.785	1.538	0.583
Two MMR doses at 5 years (1827 days)	1.091	0.813	1.463	0.564	1.115	0.782	1.590	0.547
Older sibling with likely ASD								
One MMR dose at 2 years (731 days)	0.818	0.547	1.225	0.330	0.757	0.485	1.182	0.220
One MMR dose at 3 years (1096 days)	0.837	0.584	1.200	0.333	0.807	0.542	1.202	0.292
One MMR dose at 4 years (1461 days)	0.856	0.599	1.222	0.392	0.860	0.575	1.286	0.462
One MMR dose at 5 years (1827 days)	0.875	0.591	1.296	0.505	0.917	0.582	1.443	0.708
Two MMR doses at 5 years (1827 days)	0.523	0.318	0.860	0.011	0.559	0.311	1.005	0.052

[1] N=96,054 likely/possible/no ASD index children with likely/no older sibling ASD; N=95,727 likely/no ASD index children with likely/no older sibling ASD.

[2] N=1,321 likely/possible/no ASD index children; N=994 likely/no ASD index children.

[3] Adjusted for birth year, gender, region, race/ethnicity, maternal/paternal highest education level, household income, age of mother at index infant date of birth, age of father at index infant date of birth, continuous enrollment with mental health carve-out benefit, Childhood Chronic Conditions Score, seizure, allergies, pre-term birth.

[4] Index child ASD status was classified as: Likely/possible ASD - index children with 1+ ASD diagnosis; Likely ASD – index children with 2+ ASD diagnoses; No ASD – index children with 0 ASD diagnoses.

[5] MMR vaccination doses captured after year 1 birthday.

Full model results are provided in Appendix A, Table 9

E. Discussion

Our results are fully consistent with the existing body of evidence about MMR vaccination and ASD risk. Using a large claims database of children born between 2001-2012 who have an older sibling, MMR vaccination status was **not** positively associated with a diagnosis of ASD in the entire sample of index children with older siblings or in either of the two subgroups defined by the presence or absence of ASD in the older siblings. In other words, we found no statistically significant association between MMR vaccination - either one or two doses—and ASD at any age, irrespective of the one or two claim criteria for diagnosing ASD. This lack of an association held true both before and after adjusting for continuous mental health coverage, gender, geographic region, birth year, race, parental education, household income, parental age, a modified childhood chronic conditions score, and the presence of seizures, vaccine-related allergies and pre-term birth.

In addition, the insignificant age-specific hazard ratios among younger siblings of children with ASD provide evidence suggesting that MMR vaccination is also not associated with ASD among the index children who have an older sibling with ASD. Furthermore, the results indicate that

older sibling ASD status is not a confounder of the association between index child MMR status and index child ASD risk.

There was a trend toward hazard ratios <1.0 (a negative association between MMR and ASD) for one MMR dose compared to no doses at the younger ages. At age 2, the hazard ratio was the lowest and approached statistical significance (0.793; p=0.084 in the adjusted model), suggesting the vaccine may be protective against ASD. Because there is no biological basis for thinking a vaccine could actually prevent autism, this likely reflects confounding by an external factor such as parental concerns. It is plausible, for example, that a parent who is concerned about his or her child developing autism might avoid vaccinating. And children who are already exhibiting developmental delays or other early signs of ASD during their second year of life—the time to receive the first MMR vaccination—might heighten such concerns in their parents. Thus, parental concerns are both positively associated with ASD in the child as well as an inclination NOT to vaccinate, resulting in the vaccine *appearing* –but not actually *being* – protective against autism. At older ages, after decisions about the initial MMR vaccine have already been made, and a child's developmental delays likely to be confirmed, parents may worry less about the risk specifically attributed to receiving the vaccine (for the first or second time). Accordingly, in our study, at older ages the hazard ratios for MMR vaccines approached 1.0 and were not statistically significant showing no association between vaccine and ASD in either direction, demonstrating neither protection nor risk.

In our sample of children followed since birth, the prevalence of ASD was 1% if using a 1-claim definition of ASD and 0.7% if requiring two claims with an ASD diagnosis. The risk of recurrence—defined as the risk of ASD in families in which there is already an older sibling with ASD—was 7.5% for any ASD claim(s) and 5.8% if requiring 2 claims for a diagnosis. This is comparable to the recurrence rate found in a recent study by Danish researchers and lower than the 18.7% recurrence rate that was reported by a group of researchers in the United States.[14]

The Danish study based on their national birth registry followed children born between 1980 and 2004 – approximately 1.5 million children total.[15] The researchers found that the recurrence risk varied by birth cohort (from 4.5% to 10.5%), and the overall recurrence risk was 6.1% (overall *relative* recurrence risk was 6.9%). Because the American study, by Ozonoff and colleagues, based their higher estimates of recurrence rates on a smaller clinical sample (664 children who were younger siblings of children with ASD, recruited through specialty clinics, research centers and parent groups), we believe our estimates and those of the Danish study are more reflective of the recurrence risk at the population level. Both our study and the Danish study were unable, however, to estimate recurrence among families where there is more than one older sibling with ASD, for whom recurrence rates are likely higher as demonstrated in the Ozonoff study. Furthermore, unlike the Ozonoff study, neither the Danish study nor ours address the concept of "stoppage"—that parents who have a child with ASD, especially if severe, may choose not to have any more children—into the recurrence risk estimates. If stoppage plays a significant role at the population level, our risk estimates would again be falsely low.

Despite the lack of association between MMR vaccination and ASD, there was a small but statistically significant difference (13.1% vs 12.1%) in the rate of diverse neuropsychiatric conditions that were selected as potential early markers of ASD. The higher rate of these conditions, ranging from very broad codes for "possible behavior problem" to more specific codes such as

"developmental delay" is likely another finding related to surveillance bias as children who are receiving vaccinations are also higher users of health services compared to those that are not.

This study, in its ability to use a large and recent dataset that is generally representative of the US population to construct large cohorts of children with older siblings, both with and without ASD, is both larger and more up-to-date than many comparable studies of children with ASD. The data spans an 11 year period, and the definition of ASD was validated using a chart study.[54] By examining the association in a group of children who were at increased risk of ASD (by virtue of having an older sibling with ASD) we were also able to begin to discredit the notion that there may be special subgroups of children who are susceptible to the vaccination-related neurodevelopmental adverse effects. And while a claims database cannot measure parental beliefs or reasoning for vaccination decisions, it does measure actual behaviors and does not rely on retrospective associations or parents' reports for vaccination practices or ASD diagnoses.

Administrative claims data in general and our study do have several important limitations however. Claims are generated for payment purposes, so diagnoses that do not impact services or payment are likely under-reported (e.g. mental retardation). Similarly, severity of ASD is not well-captured (e.g., degree of disability and non-verbal status rarely indicated) and may be a driver in parental beliefs and vaccination decisions, so important differences among a heterogeneous population of children were likely obscured. Lastly, and perhaps most importantly, surveillance bias almost definitely impacted our results but was difficult to control for or to quantify. Surveillance bias would, however, bias our results toward a positive association between vaccination and ASD since both are associated with greater use of health services. Thus our finding a lack of an association despite surveillance bias strengthens, rather than weakens, our results.

VI. Conclusion

A. Summary of Results

Rotavirus vaccination appeared protective against gastroenteritis but we did not find evidence supporting immunizations as protective against other infectious disease outcomes (MMR infections, meningitis, otitis media, and pneumonia). Both the lack of outcome specificity and the potential for surveillance bias were limitations in these analyses. In addition, the likely high level of baseline protection afforded by herd immunity, particularly for the rare diseases, resulted in smaller differences attributed to individual vaccination status.

The lack of association between MMR vaccination status and ASD risk we observed is consistent with and confirms the existing body of evidence on MMR immunization and ASD risk. Further, our study adds to the literature by providing the first evidence suggesting that MMR vaccination is also NOT associated with ASD among a group of children at increased risk for ASD by virtue of having an older sibling with ASD. This novel finding may help to alleviate any lingering concerns among parents and professionals that the overall safety of the MMR vaccines may not extend to particular subgroups of children.

B. Study Strengths and Limitations

The Optum Research Database is a unique data source for ASD research, affording rich, longitudinal data on disease, comorbidity, health care utilization and costs for large samples of study subjects. Using this large dataset that is reflective of the US population, we were able to construct and follow a large cohort of children with older siblings with and without evidence of ASD. Our data spans an 11 year period that is both larger and more up-to-date than many comparable studies on ASD. Furthermore, our diagnosis of ASD was validated using a chart study, generating a positive predictive value of 87% for a child with two ASD claims.

Despite the strengths of the dataset and our approach, claims data have inherent limitations because they are generated for payment, not for research. Information on diagnosis may at times be inaccurate. For example, a diagnosis submitted on a claim may be an interim or suspected diagnosis, while the patient is undergoing tests until a definitive diagnosis is established. Thus, in order to enhance accuracy in claims analysis, researchers frequently apply inclusion and exclusion criteria — for example, requiring multiple appearances of a diagnosis code over time — before considering a particular chronic condition to be present. Similarly, diagnoses that do not impact payment or that could negatively impact payment may be under-reported. There are also potential inaccuracies in the classification of sibling and other family members because of the assumptions made when identifying family relationships (Table 1) among individuals on the same health plan. In addition, there may be some misclassification of sociodemographic status, because many of the sociodemographic elements are based on algorithms (race) or are imputed (income, education) rather than directly collected; also, between 2% and 12% of the sample had missing sociodemographic data, depending on the particular variable. We conducted limited sensitivity analyses around the assignment of mothers and fathers when multiple potential mothers or fathers were identified, and found that variables such as average parental age were not meaningfully altered by selection of one potential parent versus another. Individuals with missing sociodemographic data elements were included in the multivariable analysis, and were given a separate "missing information" category for those data elements that were not complete.

Exclusion of individuals with missing information from the multivariable analysis did not substantially change the results.

Additionally, although we used claims for health care services as proxies for health behaviors, they are imperfect markers of the true drivers of health behaviors or the beliefs governing those behaviors. For example, in this study, parents' beliefs regarding vaccination efficacy and safety are important, but claims data cannot measure this directly; thus we structured our approach to use parental behaviors, vaccination receipt in the children, as a proxy for parental beliefs. We were only able to capture vaccinations for which claims were submitted, which itself is likely an underestimate of vaccinations actually received. Thus, while we cannot predict absolute vaccination rates, our comparisons among and between children in the dataset remain valid.

The severity of ASD, which undoubtedly affects health services and appearances within claims data, is inadequately captured in our data, with important clinical markers of severity like intellectual disability and non-verbal status rarely described and thus likely underreported.

Finally our mixed results on the relationship between vaccination and infectious outcomes not only shows that we were limited by the lack of information about the specific etiologic organisms implicated in the infections included, but also deepens our concerns about the role of surveillance bias and its impact, which is not yet quantified.

C. Implications and Recommendations for Future Research

The findings of this study in full, including the 4 tasks under the original contract, open a variety of important avenues for future research. Encompassing the results of all seven reports completed under this contract, feedback from researchers and project officers at NIMH, and feedback from the External Advisory Committee members, we have identified some broad topic areas that are priorities for future research using claims data. These are described below:

1. Addressing the issue of surveillance bias in claims data

Each of the reports and their results have separately raised questions about the existence of and the approach to measurement of surveillance bias as a potential constraint to using claims data. Essentially, because claims are based on the receipt of health care services and higher utilizers of health care have greater exposure to providers, they are more likely to receive diagnoses, prescriptions, treatments, and services generally. We tried to measure and control for surveillance bias in Tasks B and C (which assessed a variety of health outcomes and utilization) by controlling for preventive office visits as a proxy for general utilization (because children and adults receiving preventive visits are presumably health care "users"). In those results, controlling for preventive visits did not alter results significantly nor change conclusions. However, our more recent findings on vaccination efficacy seem to have been influenced by surveillance bias as indicated by the counterintuitive finding that some immunizations were associated with a greater, rather than lesser, risk of infection. This suggests that for certain outcomes, compared to others, surveillance bias may play a larger role and could potentially reverse the direction of an association. For health conditions or diagnoses that are milder in severity, shorter in duration, or for which care may be optional (such as upper respiratory infections or ear pain), surveillance bias seemed to play a larger role than for conditions that are chronic or result in greater impairment, such as ASD or meningitis. From our studies thus far, we believe the use of more robust analyses can account

for surveillance bias. Potential approaches that could be explored and evaluated include: restriction of outcomes on the basis of severity (e.g., requiring a hospitalization), development of measures of the propensity for health care utilization that could be used to adjust for surveillance biases, and instrumental variable approaches to control for provider-level tendencies to immunize when examining vaccination-related outcomes. Such research could demonstrate true effects of interventions such as vaccinations as well as improve methodological rigor when using claims data for outcomes research more generally.

2. Analysis of potential ASD risk factors

The Task D analysis and report from the initial years of the study explored the potential of administrative claims data for ASD risk factor research. Part of this exploration involved identifying parent-child dyads and prenatal and birth cohorts among children with (and without) ASD that can be examined for future risk factor research. We were also able to identify specific risk factors and types of risk factors that can be validly studied using claims data. Future studies could maximize available sample size and allow the implementation of more sophisticated analytic methods considering exposure and outcome timing by defining pregnancy or birth cohorts and ascertaining exposures and ASD outcomes for these cohorts rather than estimating risk factor prevelances in samples selected based on ASD case status as was done for Task D. The birth cohort identified in the second part of the study (the contract extension) could provide an initial platform for this type of analysis.

One specific risk factor of interest is the maternal use of selective serotonin reuptake inhibitors (SSRIs), with or without a diagnosis of depression. The literature thus far is inconclusive as to whether SSRI use increases risk of ASD. Also, the relatively high prevalence of depression and SSRI use indicate the public health importance of attempting to answer the question more definitively. Part of the uncertainty is related to previous studies' inability to adequately control for potential confounding by indication (i.e. inability to separate the medication effect compared with the effect of the mother's depression) which can be addressed using a large, claims-based study such as ours. In Task D, we found preliminary indications that mothers who had children with ASD had slightly higher rates of depression and SSRI use than comparison mothers and that rates of depression and SSRI use among mothers in our study were aligned with national estimates; these rates were higher than that reported in another large study that examined this risk factor in a registry from Denmark, where depression is thought to be underreported. In our dataset we have the potential ability to apply a range of tools to examine the potential of, and control for, confounding by indication to affect results, including stratification by both exposure and indication, propensity score adjustment, employment of negative controls, and instrumental variable approaches (where the instrument represents the tendency of individual providers to prescribe SSRIs to women during pregnancy). By undertaking a multipronged approach, we believe our data have the potential to significantly add to the evidence base around this question.

Another example of a risk factor/marker of high interest in autism research that can be studied using claims data is preterm birth/delivery. Much of the early evidence supporting the association between preterm birth and ASD was based on studies that use autism-risk screeners that might be expected to have a high-false positive rate in pre-term births because of the broad range of developmental issues in these children. Recently, some larger population-based studies have added to the evidence base connecting preterm birth to ASD risk, and the database we have

developed could also be quickly deployed to lend further confirmatory evidence given the accurate identification of preterm birth in claims and the large sample size.

Finally, future studies using claims data to explore potential ASD risk factors could incorporate formal validation sub-studies on both exposure and diagnosis (gathering data on exposure and diagnosis from other data sources on a fraction of the sample) that can be implemented efficiently and inexpensively compared to the time and effort needed for primary data collection. In addition to claims data, another source that can be used for validation is the Humedica electronic health record (EHR) database which itself contains moderately sized samples of children with ASD and has some overlap with the claims dataset so that there are individuals for whom both claims and EHRs are available. Such validation is similar to, but likely more efficient than, the approach taken to validate ASD in the Task A Chart Study, and would allow us to have greater confidence in the outcomes and associations we are identifying in the claims data.

3. Identification of meaningful subgroups of children with ASD, and predicting health care utilization outcomes among children with ASD.

A particular advantage of a large study such as ours for studies of children with ASD is our ability to represent and also, potentially, measure the demographic and clinical heterogeneity among children with ASD. Although ASD severity itself is poorly captured in claims, claims data includes other potentially important markers of clinical complexity or significance which cannot be studied with smaller samples. For example, seizures are an important indicator of complexity among children with ASD and may be associated with ASD severity. Outcomes could be compared between children with and without seizures. In addition, comparisons of health care utilization measures between genders among children with ASD can be examined, likely making a significant contribution to the field as current ASD research includes mostly boys. Lastly, preterm and term infants and children may have very different clinical trajectories with significant impact on health and utilization outcomes. Thus we propose identifying longitudinal cohorts of children stratified by gender, and the presence or absence of seizures and prematurity, and describing and measuring health care utilization overall and across time or age, as well as the development of undesirable and costly events such as emergency and inpatient medical hospitalizations. For older children and adolescents, for whom the clinical course is largely unmapped, characterizing clinical course, patterns of medical care (including primary care, medication use, comorbidity) would be a significant contribution to the field. Such a study might identify modifiable risk factors for adverse outcomes such as inpatient medical and psychiatric hospitalizations as well as characterize best practices in the care of older children with ASD. In addition, measuring utilization and outcomes during late adolescence and early adulthood as the individual transitions from pediatric to adult care settings may be particularly policy-relevant and is poorly understood for many children with chronic conditions, including ASD.

4. Consequences of polypharmacy

The Task C report and accompanying manuscript presented data on the extensive use of psychotropic medications and polypharmacy among children with ASD, most of which do not have proven effectiveness or safety in children. A critical next step is to use our data to look at positive and negative outcomes associated with these medications. In particular, the risk of adverse outcomes such as allergic reactions and the need for emergency care can be detected in claims data. Our rich data can be used to compare utilization patterns to treatment guidelines for mental and

behavioral health conditions where they exist and, in the absence of existence of guidelines, can be used as a foundation for assessing outcomes and subsequent guideline development. Moreover, further research into the sociodemographic and geographic variation in the practice of polypharmacy and whether the variation is driven by clinical need, access to care, access to behavioral health care, or other factors may provide a better understanding of differences in treatment patterns across the country and the need for policy analysis and intervention.

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Appendix A: Full Analysis Tables

A. Sample Comparison

Table 1. Index Child Demographic Characteristics – Comparison of A1*, B1* and C1* Study Samples with the Overall Infant Population[1]

	(1) All infants (N=1,589,371)		(O) Infants w/ an Older Sibling CE ≥6 Months (N=839,974)		(A1*) Infants CE from 0-8 Months w/ an Older Sibling CE ≥6 Months (N=601,599)		(B1*) Infants CE from 0-24 Months w/ an Older Sibling CE ≥6 Months (N=333,512)		(C1-36*) Infants CE from 0-36 Months w/ an Older Sibling CE ≥6 Months (N=218,647)		(C1-48*) Infants CE from 0-48 Months w/ an Older Sibling CE ≥6 Months (N=145,625)		(C1-60*) Infants CE from 0-60 Months w/ an Older Sibling CE ≥6 Months (N=96,054)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Birth year														
2001	136,048	8.56	73,795	8.79	53,960	8.97	31,868	9.56	21,251	9.72	15,674	10.76	11,529	12.00
2002	137,827	8.67	75,282	8.96	55,337	9.20	31,073	9.32	21,881	10.01	15,845	10.88	11,789	12.27
2003	142,733	8.98	77,292	9.20	55,387	9.21	32,048	9.61	22,743	10.40	16,425	11.28	12,475	12.99
2004	138,763	8.73	74,257	8.84	54,261	9.02	31,759	9.52	22,148	10.13	16,469	11.31	12,879	13.41
2005	153,392	9.65	81,769	9.73	57,564	9.57	33,572	10.07	24,384	11.15	18,804	12.91	14,495	15.09
2006	165,934	10.44	87,445	10.41	58,686	9.76	34,947	10.48	25,809	11.80	19,845	13.63	15,725	16.37
2007	166,744	10.49	86,633	10.31	59,036	9.81	36,599	10.97	27,577	12.61	21,503	14.77	17,162	17.87
2008	160,972	10.13	82,482	9.82	56,856	9.45	35,608	10.68	26,983	12.34	21,060	14.46	0	0.00
2009	146,496	9.22	75,196	8.95	52,913	8.80	33,925	10.17	25,871	11.83	0	0.00	0	0.00
2010	122,604	7.71	64,264	7.65	49,456	8.22	32,113	9.63	0	0.00	0	0.00	0	0.00
2011	117,858	7.42	61,559	7.33	48,143	8.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender														
Male	819,332	51.55	432,101	51.44	309,068	51.37	171,172	51.32	112,276	51.35	74,650	51.26	49,130	51.15
Female	770,039	48.45	407,873	48.56	292,531	48.63	162,340	48.68	106,371	48.65	70,975	48.74	46,924	48.85
Geographic region														
Northeast	172,089	10.83	86,376	10.28	63,848	10.61	35,858	10.75	23,643	10.81	15,975	10.97	10,610	11.05
Midwest	452,965	28.50	251,459	29.94	178,502	29.67	98,309	29.48	64,228	29.38	42,585	29.24	28,170	29.33
South	692,178	43.55	361,051	42.98	258,108	42.90	143,276	42.96	93,858	42.93	62,184	42.70	40,611	42.28

	(1) All infants (N=1,589,371)		(O) Infants w/ an Older Sibling CE ≥6 Months (N=839,974)		(A1*) Infants CE from 0-8 Months w/ an Older Sibling CE ≥6 Months (N=601,599)		(B1*) Infants CE from 0-24 Months w/ an Older Sibling CE ≥6 Months (N=333,512)		(C1-36*) Infants CE from 0-36 Months w/ an Older Sibling CE ≥6 Months (N=218,647)		(C1-48*) Infants CE from 0-48 Months w/ an Older Sibling CE ≥6 Months (N=145,625)		(C1-60*) Infants CE from 0-60 Months w/ an Older Sibling CE ≥6 Months (N=96,054)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
West	271,423	17.08	140,746	16.76	100,908	16.77	55,956	16.78	36,849	16.85	24,830	17.05	16,631	17.31
Other	716	0.05	342	0.04	233	0.04	113	0.03	69	0.03	51	0.04	32	0.03
Race/Ethnicity														
White	992,229	62.43	551,562	65.66	414,693	68.93	239,306	71.75	158,115	72.32	105,951	72.76	70,257	73.14
African-American/ Black	71,325	4.49	38,266	4.56	28,000	4.65	15,440	4.63	9,612	4.40	5,920	4.07	3,591	3.74
Native Hawaiian or Pacific Islander	1,358	0.09	709	0.08	539	0.09	292	0.09	186	0.09	120	0.08	82	0.09
American Indian or Alaskan Native	3,161	0.20	1,773	0.21	1,303	0.22	736	0.22	476	0.22	315	0.22	192	0.20
Asian	46,429	2.92	24,181	2.88	18,743	3.12	10,935	3.28	7,305	3.34	4,942	3.39	3,325	3.46
Hispanic	140,429	8.84	79,093	9.42	57,135	9.50	31,753	9.52	20,713	9.47	13,619	9.35	8,768	9.13
Other	31,486	1.98	13,810	1.64	10,667	1.77	5,971	1.79	3,825	1.75	2,534	1.74	1,647	1.71
Unknown	99,624	6.27	52,451	6.24	39,756	6.61	23,512	7.05	15,949	7.29	11,039	7.58	7,598	7.91
No SES information	203,330	12.79	78,129	9.30	30,763	5.11	5,567	1.67	2,466	1.13	1,185	0.81	594	0.62
Household income														
Under $50,000	259,052	16.30	137,779	16.40	98,019	16.29	52,858	15.85	33,140	15.16	21,084	14.48	13,300	13.85
$50,000 - $74,999	345,328	21.73	187,915	22.37	139,828	23.24	79,123	23.72	51,528	23.57	33,819	23.22	21,903	22.80
$75,000 - $99,999	273,251	17.19	156,553	18.64	120,013	19.95	71,251	21.36	47,867	21.89	32,424	22.27	21,741	22.63
$100,000 - $124,999	172,556	10.86	105,291	12.54	82,351	13.69	50,050	15.01	34,086	15.59	23,530	16.16	16,058	16.72
$125,000+	104,477	6.57	67,442	8.03	54,396	9.04	34,538	10.36	24,282	11.11	17,322	11.89	12,292	12.80
Unknown	231,377	14.56	106,865	12.72	76,229	12.67	40,125	12.03	25,278	11.56	16,261	11.17	10,166	10.58
No SES information	203,330	12.79	78,129	9.30	30,763	5.11	5,567	1.67	2,466	1.13	1,185	0.81	594	0.62

	(1) All infants (N=1,589,371)		(O) Infants w/ an Older Sibling CE ≥6 Months (N=839,974)		(A1*) Infants CE from 0-8 Months w/ an Older Sibling CE ≥6 Months (N=601,599)		(B1*) Infants CE from 0-24 Months w/ an Older Sibling CE ≥6 Months (N=333,512)		(C1-36*) Infants CE from 0-36 Months w/ an Older Sibling CE ≥6 Months (N=218,647)		(C1-48*) Infants CE from 0-48 Months w/ an Older Sibling CE ≥6 Months (N=145,625)		(C1-60*) Infants CE from 0-60 Months w/ an Older Sibling CE ≥6 Months (N=96,054)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Maternal/paternal education														
Less than 9th Grade	1,337	0.08	676	0.08	441	0.07	215	0.06	140	0.06	92	0.06	61	0.06
Less than 12th Grade	20,065	1.26	10,155	1.21	6,858	1.14	3,651	1.09	2,261	1.03	1,456	1.00	901	0.94
High School Diploma	411,232	25.87	222,387	26.48	156,953	26.09	86,692	25.99	55,974	25.60	36,447	25.03	23,608	24.58
Some college	593,787	37.36	318,521	37.92	232,257	38.61	131,927	39.56	86,359	39.50	57,348	39.38	37,513	39.05
Associate Degree	132,760	8.35	70,668	8.41	52,906	8.79	30,438	9.13	20,391	9.33	13,797	9.47	9,271	9.65
Bachelor Degree	300,555	18.91	158,941	18.92	122,028	20.28	72,299	21.68	48,686	22.27	33,487	23.00	22,795	23.73
Master Degree	4,161	0.26	2,173	0.26	1,703	0.28	1,013	0.30	688	0.31	477	0.33	318	0.33
Professional School Degree	50	0.00	22	0.00	15	0.00	8	0.00	3	0.00	2	0.00	1	0.00
Doctorate Degree	26	0.00	12	0.00	8	0.00	5	0.00	3	0.00	1	0.00	0	0.00
Unknown	19,510	1.23	10,292	1.23	7,427	1.23	4,326	1.30	2,889	1.32	1,958	1.34	1,293	1.35
No SES information	103,350	6.50	44,868	5.34	20,312	3.38	2,597	0.78	1,053	0.48	443	0.30	214	0.22
No mothers/fathers identified	2,538	0.16	1,259	0.15	691	0.11	341	0.10	200	0.09	117	0.08	79	0.08

[1] Index children with 'Possible' older sibling ASD status excluded from A1, B1, C1-36, C1-48, and C1-60

B. Infectious Disease Supplemental Results, including fully adjusted regressions

Table 2. C1-36 Bacterial Infection Event Summary - Cumulative Incidence Rates from Birth to 36 Months Stratified by Vaccination Status at 36 Months

	# subjects (N=218,647)	Bacterial Infection		Otitis Media		Pneumonia		Meningitis	
		# events from 0 to 36 months	rate per person	# events from 0 to 36 months	rate per person	# events from 0 to 36 months	rate per person	# events from 0 to 36 months	rate per person
HIB at 36 months (1096 days)									
unvaccinated	14545	21200	1.4575	20091	1.3813	1634	0.1123	38	0.0026
partially vaccinated	54316	146831	2.7033	140883	2.5938	9509	0.1751	171	0.0031
fully vaccinated	149786	444595	2.9682	429361	2.8665	24648	0.1646	445	0.0030
PCV at 36 months (1096 days)									
unvaccinated	18384	30060	1.6351	28585	1.5549	2195	0.1194	42	0.0023
partially vaccinated	51415	143451	2.7901	137640	2.6770	9166	0.1783	169	0.0033
fully vaccinated	148848	439115	2.9501	424110	2.8493	24430	0.1641	443	0.0030

unvaccinated = 0 doses by 36 months
partially vaccinated = 1, 2 or 3 doses but no 4th dose at 36 months
fully vaccinated = 4 doses by 36 months

Table 3. C1-36*[1] Relative Risk of Measles, Mumps or Rubella[2] by MMR Vaccination Level - Adjusted for Birth Year and Index Child ASD Status - No Time Interaction

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
MMR vaccination status[3]										
No	-0.009	0.991	0.795	1.236	0.939	-0.008	0.992	0.795	1.237	0.942
Yes	ref.	-	-	-	-	ref.	-	-	-	-
Index Child ASD Status										
Likely/Possible						1.063	2.894	1.632	5.132	<0.001
No						ref.	-	-	-	-
Birth year										
2001	ref.	-	-	-	-	ref.	-	-	-	-
2002	-0.400	0.670	0.469	0.957	0.028	-0.403	0.669	0.468	0.955	0.027
2003	-0.489	0.613	0.426	0.882	0.008	-0.492	0.611	0.425	0.879	0.008
2004	-0.515	0.598	0.413	0.865	0.006	-0.517	0.596	0.412	0.863	0.006
2005	-0.970	0.379	0.250	0.575	<0.001	-0.972	0.378	0.250	0.574	<0.001
2006	-0.584	0.558	0.389	0.801	0.002	-0.586	0.557	0.388	0.799	0.002
2007	-0.703	0.495	0.342	0.718	<0.001	-0.705	0.494	0.341	0.716	<0.001
2008	-0.853	0.426	0.288	0.631	<0.001	-0.851	0.427	0.289	0.632	<0.001
2009	-1.216	0.296	0.186	0.471	<0.001	-1.209	0.298	0.188	0.474	<0.001

[1] N=218,394 index children; N=253 index children had MMR event prior to year 1 birthday and have been excluded.
[2] N=408 total events across all index children.
[3] MMR vaccination captured after year 1 birthday.

Table 4. C1-36*[1] Relative Risk of Gastroenteritis[2] by RV Vaccination Level - Events 1 and 2+, Fully Adjusted Including Index Child ASD Status

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Event 1 - No rotavirus vaccination doses	0.068	1.071	1.033	1.109	<0.001	0.068	1.071	1.033	1.110	<0.001
Event 1 - Any rotavirus vaccination doses	ref.	-	-	-	-	ref.	-	-	-	-
Events 2+ - No rotavirus vaccination doses	-0.045	0.956	0.888	1.029	0.229	-0.044	0.957	0.889	1.030	0.244
Events 2+ - Any rotavirus vaccination doses	ref.	-	-	-	-	ref.	-	-	-	-
Index Child ASD Status										
Likely/Possible						0.240	1.271	1.112	1.453	<0.001
No						ref.	-	-	-	-
Birth year										
2006	ref.	-	-	-	-	ref.	-	-	-	-
2007	-0.107	0.899	0.864	0.935	<0.001	-0.107	0.899	0.864	0.935	<0.001
2008	-0.170	0.843	0.808	0.881	<0.001	-0.170	0.844	0.808	0.881	<0.001
2009	-0.283	0.754	0.720	0.790	<0.001	-0.281	0.755	0.720	0.791	<0.001
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-0.105	0.901	0.875	0.927	<0.001	-0.102	0.903	0.877	0.930	<0.001
Region										
Northeast	-0.315	0.730	0.692	0.770	<0.001	-0.317	0.729	0.691	0.768	<0.001
Midwest	-0.458	0.633	0.608	0.658	<0.001	-0.457	0.633	0.608	0.659	<0.001
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.218	0.804	0.772	0.838	<0.001	-0.217	0.805	0.772	0.839	<0.001
Other	0.268	1.307	0.629	2.717	0.473	0.268	1.307	0.629	2.718	0.473

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	-0.074	0.929	0.870	0.992	0.028	-0.074	0.929	0.870	0.992	0.027
Asian	0.032	1.032	0.953	1.118	0.432	0.032	1.032	0.953	1.118	0.436
Hispanic	0.272	1.312	1.255	1.372	<0.001	0.272	1.312	1.255	1.372	<0.001
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	0.250	1.284	1.177	1.400	<0.001	0.250	1.285	1.177	1.401	<0.001
Unknown/No SES information	0.007	1.007	0.950	1.068	0.808	0.007	1.007	0.950	1.067	0.813
Maternal/paternal education[3]										
Less than high school diploma	0.050	1.051	0.926	1.194	0.442	0.050	1.052	0.926	1.195	0.438
High school diploma	0.010	1.010	0.972	1.050	0.612	0.010	1.010	0.972	1.050	0.613
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	-0.030	0.970	0.917	1.026	0.285	-0.031	0.969	0.917	1.025	0.275
Bachelor/Master/Professional/Doctorate degree	-0.010	0.990	0.946	1.036	0.660	-0.010	0.990	0.946	1.036	0.657
Unknown/No SES information/No parents identified	-0.006	0.994	0.880	1.124	0.926	-0.004	0.996	0.881	1.126	0.948
Household income										
Under $50,000	-0.014	0.986	0.941	1.034	0.571	-0.013	0.987	0.941	1.034	0.578
$50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	-0.037	0.964	0.921	1.008	0.104	-0.037	0.964	0.922	1.008	0.107
$100,000 - $124,999	-0.016	0.985	0.933	1.039	0.573	-0.015	0.985	0.933	1.040	0.580
$125,000+	0.028	1.029	0.961	1.102	0.416	0.029	1.029	0.961	1.102	0.411
Unknown/No SES information	-0.001	0.999	0.952	1.049	0.970	-0.001	0.999	0.952	1.049	0.976

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Age of mother at infant date of birth										
<20	0.385	1.469	1.036	2.083	0.031	0.388	1.473	1.039	2.090	0.030
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.013	0.987	0.946	1.030	0.555	-0.012	0.988	0.946	1.031	0.569
35-39	-0.054	0.948	0.900	0.998	0.042	-0.054	0.948	0.900	0.998	0.042
40-49	-0.113	0.893	0.823	0.970	0.007	-0.114	0.892	0.822	0.969	0.007
Multiple	0.095	1.100	1.031	1.172	0.004	0.095	1.100	1.031	1.173	0.004
Unknown Age Categorization	0.047	1.048	0.957	1.149	0.312	0.047	1.048	0.957	1.149	0.312
Age of father at infant date of birth										
<20	0.255	1.291	0.915	1.820	0.146	0.256	1.292	0.916	1.823	0.145
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.028	0.972	0.926	1.021	0.265	-0.028	0.972	0.925	1.021	0.259
35-39	-0.006	0.994	0.941	1.050	0.830	-0.007	0.993	0.940	1.049	0.808
40-49	-0.008	0.992	0.931	1.058	0.818	-0.009	0.991	0.930	1.057	0.790
Multiple	0.080	1.083	1.000	1.174	0.051	0.078	1.081	0.998	1.172	0.056
Unknown Age Categorization	-0.012	0.988	0.921	1.061	0.747	-0.011	0.989	0.921	1.061	0.751
Seizures[4]	0.260	1.297	1.212	1.388	<0.001	0.248	1.281	1.197	1.371	<0.001
Allergies[4]	0.266	1.304	1.160	1.467	<0.001	0.263	1.300	1.156	1.463	<0.001
Pre-term birth[4]	0.121	1.129	1.074	1.187	<0.001	0.119	1.127	1.072	1.184	<0.001

[1] N=106,240 index children born during or after 2006.
[2] N=19,693 gastroenteritis events.
[3] Highest level among all mothers/fathers.
[4] Captured during each index child's entire enrollment period.

Table 5. C1-36*[1] Relative Risk of Otitis Media[2] by Categorical HIB/PCV Vaccination Level, Fully Adjusted Including Index Child ASD Status

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
HIB vaccination status										
Unvaccinated	-0.386	0.680	0.662	0.698	<0.001	-0.386	0.680	0.662	0.698	<0.001
Partially Vaccinated	-0.026	0.974	0.965	0.984	<0.001	-0.026	0.975	0.965	0.984	<0.001
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
PCV vaccination status										
Unvaccinated	-0.257	0.773	0.756	0.791	<0.001	-0.258	0.773	0.756	0.791	<0.001
Partially Vaccinated	-0.047	0.954	0.945	0.963	<0.001	-0.047	0.954	0.945	0.963	<0.001
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
Index Child ASD Status										
Likely/Possible						0.179	1.197	1.153	1.241	<0.001
No						ref.	-	-	-	-
Birth year										
2001	ref.	-	-	-	-	ref.	-	-	-	-
2002	-0.041	0.960	0.944	0.976	<0.001	-0.041	0.959	0.943	0.976	<0.001
2003	-0.065	0.937	0.921	0.953	<0.001	-0.065	0.937	0.921	0.953	<0.001
2004	-0.087	0.916	0.901	0.932	<0.001	-0.088	0.916	0.901	0.932	<0.001
2005	-0.131	0.877	0.863	0.892	<0.001	-0.131	0.877	0.863	0.892	<0.001
2006	-0.127	0.881	0.866	0.896	<0.001	-0.127	0.881	0.866	0.895	<0.001
2007	-0.144	0.866	0.852	0.881	<0.001	-0.144	0.866	0.852	0.881	<0.001
2008	-0.144	0.866	0.852	0.881	<0.001	-0.144	0.866	0.852	0.881	<0.001
2009	-0.165	0.848	0.834	0.863	<0.001	-0.164	0.849	0.834	0.863	<0.001
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-0.105	0.901	0.894	0.908	<0.001	-0.102	0.903	0.896	0.910	<0.001

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Region										
Northeast	-0.124	0.883	0.871	0.896	<0.001	-0.125	0.882	0.870	0.895	<0.001
Midwest	-0.095	0.909	0.901	0.917	<0.001	-0.095	0.909	0.901	0.917	<0.001
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.308	0.735	0.726	0.744	<0.001	-0.308	0.735	0.726	0.744	<0.001
Other	-0.630	0.532	0.366	0.776	0.001	-0.629	0.533	0.366	0.776	0.001
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	-0.302	0.740	0.724	0.756	<0.001	-0.301	0.740	0.724	0.756	<0.001
Asian	-0.555	0.574	0.558	0.591	<0.001	-0.555	0.574	0.558	0.590	<0.001
Hispanic	-0.099	0.906	0.893	0.918	<0.001	-0.099	0.905	0.893	0.918	<0.001
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	-0.127	0.880	0.856	0.905	<0.001	-0.128	0.880	0.856	0.905	<0.001
Unknown/No SES information	-0.059	0.942	0.929	0.956	<0.001	-0.059	0.942	0.929	0.956	<0.001
Maternal/paternal education[3]										
Less than high school diploma	-0.043	0.958	0.919	0.999	0.044	-0.042	0.958	0.919	0.999	0.046
High school diploma	0.024	1.024	1.013	1.035	<0.001	0.024	1.024	1.013	1.035	<0.001
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	0.007	1.007	0.993	1.022	0.326	0.007	1.007	0.993	1.021	0.354
Bachelor/Master/Professional/Doctorate degree	-0.028	0.973	0.961	0.985	<0.001	-0.028	0.973	0.961	0.985	<0.001
Unknown/No SES information/No parents identified	-0.007	0.993	0.962	1.025	0.670	-0.006	0.994	0.963	1.026	0.713
Household income										
Under $50,000	-0.005	0.995	0.982	1.008	0.453	-0.005	0.995	0.982	1.008	0.464
$50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	0.040	1.040	1.028	1.053	<0.001	0.040	1.041	1.028	1.053	<0.001
$100,000 - $124,999	0.061	1.062	1.048	1.077	<0.001	0.061	1.063	1.048	1.077	<0.001

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
$125,000+	0.063	1.065	1.047	1.083	<0.001	0.063	1.065	1.047	1.084	<0.001
Unknown/No SES information	-0.032	0.968	0.954	0.982	<0.001	-0.033	0.968	0.954	0.982	<0.001
Age of mother at infant date of birth										
<20	-0.152	0.859	0.781	0.944	0.002	-0.151	0.860	0.782	0.945	0.002
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	0.036	1.037	1.025	1.049	<0.001	0.036	1.037	1.025	1.048	<0.001
35-39	0.014	1.014	1.000	1.028	0.042	0.014	1.014	1.000	1.028	0.047
40-49	-0.042	0.958	0.937	0.980	<0.001	-0.043	0.958	0.937	0.979	<0.001
Multiple	0.014	1.014	0.997	1.032	0.107	0.014	1.014	0.997	1.032	0.114
Unknown Age Categorization	0.018	1.018	0.992	1.046	0.183	0.018	1.018	0.992	1.046	0.180
Age of father at infant date of birth										
<20	-0.097	0.907	0.808	1.019	0.100	-0.097	0.908	0.809	1.020	0.103
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	0.011	1.011	0.998	1.025	0.087	0.011	1.011	0.998	1.025	0.085
35-39	-0.009	0.991	0.977	1.006	0.234	-0.009	0.991	0.977	1.005	0.223
40-49	-0.060	0.942	0.926	0.958	<0.001	-0.061	0.941	0.925	0.957	<0.001
Multiple	0.035	1.036	1.014	1.058	0.001	0.035	1.035	1.013	1.058	0.001
Unknown Age Categorization	-0.029	0.971	0.951	0.992	0.006	-0.029	0.971	0.952	0.992	0.006
Seizures[4]	0.181	1.199	1.177	1.221	<0.001	0.171	1.187	1.164	1.209	<0.001
Allergies[4]	0.168	1.183	1.135	1.234	<0.001	0.166	1.181	1.133	1.231	<0.001
Pre-term birth[5]	0.071	1.074	1.059	1.089	<0.001	0.070	1.072	1.057	1.087	<0.001

[1] N=218,647 index children.
[2] N=790,767 otitis media events.
[3] Highest level among all mothers/fathers.
[4] Captured between birth and 24 months of age.
[5] Captured during each index child's entire enrollment period.

Table 6. C1-36*1 Relative Risk of Pneumonia2 by Categorical HIB/PCV Vaccination Level, Fully Adjusted Including Index Child ASD Status

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
HIB vaccination status										
Unvaccinated	-0.174	0.841	0.768	0.921	<0.001	-0.174	0.841	0.768	0.921	<0.001
Partially Vaccinated	0.014	1.014	0.983	1.047	0.383	0.014	1.014	0.983	1.047	0.382
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
PCV vaccination status										
Unvaccinated	-0.137	0.872	0.794	0.958	0.004	-0.137	0.872	0.794	0.958	0.004
Partially Vaccinated	-0.058	0.944	0.914	0.975	<0.001	-0.058	0.944	0.914	0.975	<0.001
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
Index Child ASD Status										
Likely/Possible						0.013	1.013	0.903	1.138	0.822
No						ref.	-	-	-	-
Birth year										
2001	ref.	-	-	-	-	ref.	-	-	-	-
2002	0.017	1.017	0.964	1.073	0.534	0.017	1.017	0.964	1.073	0.535
2003	0.014	1.014	0.964	1.067	0.584	0.014	1.014	0.964	1.067	0.585
2004	-0.029	0.971	0.924	1.020	0.242	-0.029	0.971	0.924	1.020	0.242
2005	-0.020	0.981	0.931	1.033	0.458	-0.020	0.981	0.931	1.033	0.458
2006	-0.002	0.998	0.950	1.048	0.926	-0.002	0.998	0.950	1.048	0.926
2007	0.003	1.003	0.951	1.059	0.908	0.003	1.003	0.951	1.059	0.908
2008	-0.010	0.990	0.942	1.041	0.695	-0.010	0.990	0.942	1.041	0.696
2009	-0.076	0.927	0.880	0.977	0.005	-0.076	0.927	0.880	0.977	0.005
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-0.140	0.870	0.849	0.891	<0.001	-0.140	0.870	0.849	0.891	<0.001

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Region										
Northeast	0.018	1.019	0.981	1.058	0.343	0.018	1.018	0.981	1.058	0.346
Midwest	0.082	1.085	1.056	1.115	<0.001	0.082	1.085	1.056	1.115	<0.001
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.072	0.930	0.893	0.969	<0.001	-0.072	0.930	0.893	0.969	<0.001
Other	-0.300	0.741	0.381	1.442	0.377	-0.300	0.741	0.381	1.442	0.377
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	-0.059	0.943	0.893	0.996	0.034	-0.059	0.943	0.893	0.996	0.035
Asian	0.128	1.136	1.064	1.214	<0.001	0.128	1.136	1.064	1.214	<0.001
Hispanic	0.038	1.038	0.996	1.083	0.079	0.038	1.038	0.996	1.083	0.079
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	0.138	1.148	1.068	1.234	<0.001	0.138	1.148	1.068	1.234	<0.001
Unknown/No SES information	-0.007	0.993	0.955	1.034	0.744	-0.007	0.993	0.955	1.034	0.744
Maternal/paternal education[3]										
Less than high school diploma	-0.041	0.960	0.857	1.075	0.477	-0.041	0.960	0.857	1.075	0.477
High school diploma	0.029	1.029	0.994	1.067	0.108	0.029	1.029	0.994	1.067	0.108
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	-0.055	0.947	0.907	0.988	0.012	-0.055	0.947	0.907	0.988	0.012
Bachelor/Master/Professional/Doctorate degree	-0.056	0.945	0.912	0.980	0.002	-0.056	0.945	0.912	0.980	0.002
Unknown/No SES information/No parents identified	-0.021	0.979	0.897	1.068	0.632	-0.021	0.979	0.897	1.068	0.633
Household income										
Under $50,000	0.055	1.056	1.015	1.099	0.007	0.055	1.056	1.015	1.099	0.007
$50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	0.009	1.009	0.972	1.048	0.623	0.009	1.009	0.972	1.048	0.623
$100,000 - $124,999	0.016	1.017	0.974	1.061	0.454	0.016	1.017	0.974	1.061	0.454

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
$125,000+	0.035	1.036	0.986	1.088	0.162	0.035	1.036	0.986	1.088	0.162
Unknown/No SES information	0.026	1.027	0.978	1.078	0.291	0.026	1.026	0.978	1.078	0.291
Age of mother at infant date of birth										
<20	-0.270	0.763	0.560	1.040	0.087	-0.270	0.763	0.560	1.040	0.087
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.024	0.976	0.945	1.008	0.144	-0.024	0.976	0.945	1.008	0.144
35-39	-0.040	0.961	0.924	1.000	0.051	-0.040	0.961	0.924	1.000	0.051
40-49	-0.094	0.910	0.857	0.967	0.002	-0.094	0.910	0.857	0.967	0.002
Multiple	0.009	1.009	0.955	1.065	0.760	0.009	1.009	0.955	1.065	0.761
Unknown Age Categorization	0.022	1.022	0.942	1.109	0.603	0.022	1.022	0.942	1.109	0.603
Age of father at infant date of birth										
<20	-0.024	0.976	0.687	1.387	0.893	-0.024	0.976	0.687	1.387	0.893
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	0.021	1.021	0.983	1.061	0.291	0.021	1.021	0.983	1.061	0.291
35-39	0.017	1.017	0.976	1.060	0.424	0.017	1.017	0.976	1.060	0.425
40-49	0.008	1.008	0.955	1.063	0.775	0.008	1.008	0.955	1.063	0.777
Multiple	0.055	1.056	0.981	1.137	0.146	0.055	1.056	0.981	1.137	0.146
Unknown Age Categorization	0.063	1.065	1.006	1.126	0.029	0.063	1.065	1.006	1.126	0.029
Seizures[4]	0.603	1.827	1.725	1.934	<0.001	0.602	1.826	1.724	1.933	<0.001
Allergies[4]	0.680	1.974	1.684	2.315	<0.001	0.680	1.974	1.683	2.315	<0.001
Pre-term birth[5]	0.502	1.652	1.583	1.723	<0.001	0.502	1.651	1.583	1.723	<0.001

[1] N=218,647 index children.
[2] N=56,178 pneumonia events.
[3] Highest level among all mothers/fathers.
[4] Captured between birth and 24 months of age.
[5] Captured during each index child's entire enrollment period.

Table 7. C1-36*1 Relative Risk of Meningitis2 by Categorical HIB/PCV Vaccination Level, Fully Adjusted Including Index Child ASD Status

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
HIB vaccination status										
Unvaccinated	0.522	1.685	0.594	4.780	0.326	0.523	1.687	0.594	4.792	0.326
Partially Vaccinated	0.331	1.392	0.854	2.269	0.185	0.330	1.390	0.853	2.266	0.186
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
PCV vaccination status										
Unvaccinated	-0.257	0.774	0.317	1.889	0.573	-0.259	0.772	0.316	1.886	0.570
Partially Vaccinated	-0.251	0.778	0.478	1.268	0.314	-0.250	0.779	0.478	1.268	0.315
Fully Vaccinated	ref.	-	-	-	-	ref.	-	-	-	-
Index Child ASD Status										
Likely/Possible						-0.850	0.427	0.192	0.950	0.037
No						ref.	-	-	-	-
Birth year										
2001										
2002	-0.177	0.837	0.568	1.234	0.370	-0.174	0.840	0.570	1.239	0.380
2003	-0.140	0.869	0.634	1.191	0.384	-0.135	0.874	0.638	1.198	0.403
2004	-0.133	0.876	0.580	1.322	0.528	-0.131	0.877	0.581	1.324	0.534
2005	-0.551	0.576	0.411	0.809	0.001	-0.549	0.577	0.411	0.810	0.002
2006	-0.308	0.735	0.528	1.022	0.067	-0.307	0.736	0.529	1.024	0.069
2007	-0.763	0.466	0.317	0.685	<0.001	-0.764	0.466	0.317	0.684	<0.001
2008	-0.635	0.530	0.372	0.754	<0.001	-0.638	0.528	0.371	0.752	<0.001
2009	-0.751	0.472	0.309	0.720	<0.001	-0.754	0.470	0.308	0.717	<0.001
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-0.183	0.832	0.691	1.003	0.054	-0.196	0.822	0.682	0.990	0.039

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
Region										
Northeast	0.171	1.187	0.902	1.562	0.222	0.179	1.196	0.909	1.573	0.201
Midwest	-0.603	0.547	0.439	0.683	<0.001	-0.604	0.546	0.438	0.682	<0.001
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.317	0.728	0.531	0.998	0.049	-0.320	0.726	0.530	0.995	0.047
Other	-8.614	0.000	0.000	0.000	<0.001	-8.615	0.000	0.000	0.000	<0.001
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	0.124	1.132	0.764	1.677	0.535	0.121	1.129	0.762	1.671	0.546
Asian	0.237	1.267	0.557	2.883	0.573	0.236	1.266	0.557	2.877	0.574
Hispanic	0.164	1.178	0.890	1.561	0.253	0.165	1.179	0.890	1.562	0.251
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	-0.745	0.475	0.223	1.012	0.054	-0.746	0.474	0.223	1.011	0.053
Unknown/No SES information	-0.023	0.977	0.722	1.321	0.879	-0.026	0.975	0.721	1.318	0.867
Maternal/paternal education[3]										
Less than high school diploma	-0.324	0.723	0.328	1.593	0.421	-0.332	0.717	0.326	1.581	0.410
High school diploma	-0.030	0.971	0.770	1.223	0.800	-0.032	0.968	0.769	1.220	0.785
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	-0.486	0.615	0.427	0.887	0.009	-0.483	0.617	0.428	0.889	0.010
Bachelor/Master/Professional/Doctorate degree	0.097	1.102	0.775	1.568	0.589	0.094	1.098	0.772	1.562	0.603
Unknown/No SES information/No parents identified	0.147	1.158	0.584	2.296	0.675	0.140	1.151	0.580	2.282	0.688
Household income										
Under $50,000	-0.015	0.985	0.740	1.310	0.915	-0.019	0.981	0.738	1.306	0.898
50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	0.053	1.054	0.795	1.398	0.714	0.051	1.052	0.793	1.394	0.725
$100,000 - $124,999	0.170	1.185	0.811	1.733	0.380	0.172	1.188	0.813	1.736	0.374

Covariate	Index Child ASD Status									
	Unadjusted for index child ASD status					Adjusted for index child ASD status				
	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value	Estimate	Hazard Ratio	Wald lower 95% CI	Wald upper 95% CI	p-value
$125,000+	-0.027	0.974	0.636	1.491	0.902	-0.028	0.972	0.635	1.489	0.897
Unknown/No SES information	0.045	1.046	0.778	1.405	0.767	0.045	1.046	0.778	1.405	0.767
Age of mother at infant date of birth										
<20	0.799	2.224	0.758	6.523	0.146	0.806	2.239	0.766	6.546	0.141
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.035	0.965	0.738	1.262	0.796	-0.035	0.965	0.738	1.262	0.796
35-39	-0.001	0.999	0.747	1.336	0.992	-0.001	0.999	0.747	1.335	0.993
40-49	0.083	1.086	0.714	1.653	0.700	0.087	1.091	0.717	1.660	0.686
Multiple	0.144	1.155	0.830	1.606	0.393	0.145	1.156	0.831	1.608	0.390
Unknown Age Categorization	0.177	1.193	0.638	2.232	0.581	0.177	1.194	0.638	2.233	0.580
Age of father at infant date of birth										
<20	-0.271	0.762	0.112	5.192	0.782	-0.263	0.768	0.113	5.219	0.788
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.057	0.945	0.712	1.252	0.692	-0.057	0.944	0.712	1.252	0.690
35-39	-0.258	0.772	0.556	1.073	0.123	-0.257	0.773	0.557	1.074	0.125
40-49	-0.243	0.784	0.550	1.117	0.178	-0.240	0.787	0.552	1.121	0.185
Multiple	-0.414	0.661	0.415	1.051	0.080	-0.411	0.663	0.417	1.055	0.083
Unknown Age Categorization	-0.063	0.939	0.635	1.386	0.750	-0.064	0.938	0.635	1.385	0.748
Seizures[4]	2.105	8.205	6.323	10.647	<0.001	2.138	8.482	6.521	11.032	<0.001
Allergies[4]	0.710	2.033	1.003	4.120	0.049	0.744	2.104	1.039	4.257	0.039
Pre-term birth[4]	0.663	1.940	1.524	2.469	<0.001	0.672	1.957	1.539	2.490	<0.001

[1] N=218,647 index children.
[2] N=721 meningitis events.
[3] Highest level among all mothers/fathers.
[4] Captured during each index child's entire enrollment period.

C. Fully Adjusted ASD outcome Regressions

Table 8. C1-60*1 Relative Risk of ASD2 by Index Child MMR Vaccination Status, Fully Adjusted with Time Interaction

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
MMR vaccination doses[3]										
0	ref.	-	-	-	-	ref.	-	-	-	-
1	-0.223	0.800	0.515	1.242	0.321	-0.374	0.688	0.416	1.138	0.145
2	-1.119	0.326	0.147	0.727	0.006	-1.416	0.243	0.098	0.601	0.002
MMR vaccination doses[3] - time interaction										
0	ref.	-	-	-	-	ref.	-	-	-	-
1	0.000	1.000	1.000	1.000	0.628	0.000	1.000	1.000	1.001	0.328
2	0.001	1.001	1.000	1.001	0.014	0.001	1.001	1.000	1.001	0.004
Birth year										
2001	ref.	-	-	-	-	ref.	-	-	-	-
2002	0.058	1.059	0.858	1.309	0.592	0.206	1.228	0.961	1.570	0.100
2003	0.103	1.109	0.901	1.363	0.329	0.243	1.275	1.001	1.625	0.049
2004	0.069	1.072	0.868	1.323	0.519	0.197	1.218	0.953	1.557	0.116
2005	0.032	1.032	0.835	1.276	0.770	0.087	1.091	0.849	1.403	0.496
2006	0.080	1.083	0.879	1.334	0.454	0.073	1.075	0.836	1.383	0.572
2007	0.234	1.264	1.026	1.556	0.027	0.278	1.321	1.032	1.689	0.027
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-1.215	0.297	0.260	0.339	<0.001	-1.346	0.260	0.222	0.305	<0.001
Region										
Northeast	0.280	1.323	1.123	1.560	<0.001	0.299	1.349	1.115	1.632	0.002
Midwest	0.067	1.069	0.937	1.220	0.321	0.121	1.129	0.969	1.315	0.120
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.086	0.917	0.779	1.080	0.300	-0.086	0.918	0.760	1.109	0.375

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Other	-8.308	0.000	0.000	0.000	<0.001	-8.608	0.000	0.000	0.000	<0.001
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	-0.253	0.777	0.558	1.082	0.135	-0.450	0.637	0.419	0.969	0.035
Asian	0.062	1.064	0.799	1.418	0.671	0.057	1.059	0.764	1.468	0.732
Hispanic	0.080	1.083	0.892	1.316	0.420	0.047	1.049	0.836	1.316	0.682
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	0.101	1.106	0.772	1.583	0.583	0.086	1.090	0.725	1.637	0.679
Unknown/No SES information	0.059	1.061	0.878	1.281	0.539	-0.048	0.953	0.761	1.193	0.674
Maternal/paternal education[4]										
Less than high school diploma	0.092	1.096	0.636	1.891	0.741	-0.081	0.922	0.464	1.833	0.817
High school diploma	-0.150	0.860	0.733	1.010	0.066	-0.142	0.867	0.723	1.041	0.126
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	0.130	1.139	0.949	1.366	0.163	0.213	1.237	1.008	1.518	0.041
Bachelor/Master/Professional/Doctorate degree	-0.041	0.960	0.817	1.128	0.621	-0.056	0.945	0.785	1.139	0.555
Unknown/No SES information/No parents identified	-0.516	0.597	0.347	1.026	0.062	-0.372	0.689	0.383	1.242	0.215
Household income										
Under $50,000	0.012	1.012	0.828	1.237	0.908	0.008	1.008	0.795	1.277	0.950
$50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	-0.074	0.929	0.785	1.098	0.386	-0.004	0.996	0.822	1.206	0.968
$100,000 - $124,999	0.054	1.055	0.875	1.274	0.573	0.077	1.080	0.871	1.340	0.482
$125,000+	-0.024	0.977	0.779	1.225	0.839	-0.001	0.999	0.770	1.296	0.995
Unknown/No SES information	0.092	1.096	0.899	1.336	0.364	0.135	1.145	0.911	1.438	0.246

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Age of mother at infant date of birth										
<20	-0.582	0.559	0.080	3.885	0.557	-0.268	0.765	0.109	5.375	0.788
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.003	0.997	0.842	1.181	0.976	-0.026	0.974	0.804	1.181	0.793
35-39	0.046	1.047	0.860	1.274	0.646	-0.034	0.967	0.773	1.210	0.768
40-49	0.338	1.402	1.077	1.825	0.012	0.177	1.193	0.880	1.618	0.255
Multiple	0.150	1.161	0.923	1.461	0.202	0.125	1.133	0.872	1.473	0.349
Unknown Age Categorization	-0.160	0.852	0.542	1.339	0.487	-0.262	0.770	0.449	1.321	0.343
Age of father at infant date of birth										
<20	-0.426	0.653	0.102	4.172	0.652	-0.037	0.963	0.152	6.116	0.969
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.057	0.945	0.776	1.151	0.574	0.002	1.002	0.795	1.263	0.988
35-39	0.068	1.071	0.865	1.326	0.532	0.205	1.228	0.956	1.577	0.108
40-49	0.212	1.236	0.980	1.560	0.074	0.364	1.440	1.100	1.884	0.008
Multiple	0.161	1.175	0.880	1.568	0.274	0.333	1.396	1.007	1.935	0.045
Unknown Age Categorization	0.001	1.001	0.737	1.359	0.995	0.134	1.144	0.803	1.629	0.456
Mental health benefits[5]	0.095	1.099	0.925	1.307	0.284	0.026	1.026	0.842	1.249	0.800
Childhood Chronic Conditions Score (modified)[6]	0.243	1.275	1.197	1.359	<0.001	0.206	1.229	1.140	1.325	<0.001
Seizures[7]	1.734	5.662	4.965	6.457	<0.001	1.826	6.208	5.340	7.218	<0.001
Allergies[7]	0.521	1.684	1.161	2.444	0.006	0.513	1.670	1.080	2.580	0.021
Pre-term birth[7]	0.348	1.417	1.206	1.664	<0.001	0.317	1.373	1.138	1.657	<0.001
Time/Age specific hazards ratios										
One MMR dose at 1 years (365 days)	-0.193	0.824	0.591	1.149	0.254	-0.303	0.738	0.507	1.075	0.114
One MMR dose at 2 years (731 days)	-0.163	0.849	0.671	1.076	0.176	-0.232	0.793	0.609	1.032	0.084
One MMR dose at 3 years (1096 days)	-0.134	0.875	0.735	1.042	0.134	-0.161	0.851	0.700	1.035	0.106
One MMR dose at 4 years (1461 days)	-0.104	0.901	0.750	1.084	0.270	-0.090	0.914	0.735	1.136	0.416
One MMR dose at 5 years (1827 days)	-0.074	0.929	0.717	1.202	0.574	-0.019	0.981	0.718	1.340	0.904

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Two MMR doses at 3 years (1096 days)	-0.516	0.597	0.408	0.875	0.008	-0.619	0.538	0.346	0.837	0.006
Two MMR doses at 4 years (1461 days)	-0.314	0.730	0.546	0.976	0.034	-0.354	0.702	0.497	0.992	0.045
Two MMR doses at 5 years (1827 days)	-0.113	0.894	0.680	1.175	0.420	-0.088	0.916	0.657	1.278	0.607

[1] N=96,054 likely/possible/no ASD index children with likely/no older sibling ASD; N=95,727 likely/no ASD index children with likely/no older sibling ASD.
[2] N=1,321 likely/possible/no ASD index children; N=994 likely/no ASD index children.
[3] MMR vaccination doses captured after year 1 birthday.
[4] Highest level among all mothers/fathers.
[5] Continuously enrolled with mental health benefits from birth to at least 60 months of age.
[6] Captured between birth and 24 months of age..
[7] Captured during each index child's entire enrollment period.

Table 9. C1-60*[1] Relative Risk of ASD[2] by Index Child MMR Vaccination Status, Fully Adjusted with Time Interaction, Older Sibling ASD Status, and Older Sibling ASD Status Interacted with MMR Vaccination Status

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
MMR vaccination doses[3]										
0	ref.	-	-	-	-	ref.	-	-	-	-
1	-0.070		0.595	1.461	0.761	-0.225		0.478	1.334	0.390
2	-0.911		0.178	0.908	0.028	-1.231		0.116	0.734	0.009
MMR vaccination doses[3] - time interaction										
0	ref.	-	-	-	-	ref.	-	-	-	-
1	0.000		1.000	1.000	0.721	0.000		1.000	1.001	0.386
2	0.001		1.000	1.001	0.017	0.001		1.000	1.001	0.005
Older sibling ASD Status										
Likely	2.015		5.294	0.628	<0.001	2.084		5.456	1.840	0.000
No	ref.	-	-	-	-	ref.	-	-	-	-
MMR vaccination doses[3] - older sibling ASD = likely										
0	ref.	-	-	-	-	ref.	-	-	-	-
1	-0.175		0.562	1.254	0.392	-0.181		0.534	1.305	0.428
2	-0.734		0.290	0.794	0.004	-0.691		0.280	0.897	0.020
Birth year										
2001	ref.	-	-	-	-	ref.	-	-	-	-
2002	0.059	1.060	0.858	1.311	0.588	0.209	1.232	0.963	1.577	0.097
2003	0.095	1.100	0.894	1.353	0.366	0.243	1.276	1.000	1.627	0.050
2004	0.049	1.050	0.850	1.298	0.649	0.177	1.193	0.932	1.528	0.161
2005	0.007	1.007	0.815	1.246	0.945	0.062	1.064	0.827	1.368	0.629
2006	0.048	1.049	0.851	1.294	0.653	0.041	1.042	0.808	1.342	0.752
2007	0.198	1.219	0.989	1.503	0.063	0.251	1.285	1.003	1.645	0.047

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Gender										
Male	ref.	-	-	-	-	ref.	-	-	-	-
Female	-1.209	0.299	0.262	0.341	<0.001	-1.341	0.262	0.223	0.306	0.000
Region										
Northeast	0.260	1.297	1.100	1.529	0.002	0.278	1.321	1.091	1.599	0.004
Midwest	0.053	1.055	0.924	1.204	0.432	0.107	1.113	0.955	1.296	0.170
South	ref.	-	-	-	-	ref.	-	-	-	-
West	-0.087	0.916	0.778	1.079	0.294	-0.089	0.915	0.757	1.105	0.354
Other	-8.301	0.000	0.000	0.000	<0.001	-8.535	0.000	0.000	0.000	0.000
Race/Ethnicity										
White	ref.	-	-	-	-	ref.	-	-	-	-
African-American/Black	-0.191	0.826	0.593	1.151	0.259	-0.383	0.682	0.448	1.037	0.074
Asian	0.089	1.093	0.823	1.450	0.540	0.079	1.082	0.785	1.492	0.631
Hispanic	0.115	1.121	0.923	1.363	0.249	0.084	1.087	0.866	1.365	0.470
Other/Native Hawaiian or Pacific Islander/American Indian or Alaskan Native	0.087	1.091	0.768	1.549	0.627	0.059	1.061	0.715	1.574	0.770
Unknown/No SES information	0.074	1.077	0.891	1.303	0.443	-0.036	0.964	0.769	1.209	0.752
Maternal/paternal education[4]										
Less than high school diploma	0.128	1.137	0.655	1.971	0.649	-0.048	0.954	0.477	1.908	0.893
High school diploma	-0.139	0.870	0.742	1.021	0.088	-0.132	0.876	0.730	1.051	0.155
Some college	ref.	-	-	-	-	ref.	-	-	-	-
Associate degree	0.137	1.146	0.954	1.377	0.144	0.234	1.264	1.030	1.551	0.025
Bachelor/Master/Professional/Doctorate degree	-0.060	0.942	0.801	1.107	0.467	-0.076	0.927	0.768	1.118	0.425
Unknown/No SES information/No parents identified	-0.482	0.617	0.360	1.058	0.079	-0.340	0.712	0.397	1.277	0.254

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Household income										
Under $50,000	0.010	1.010	0.827	1.232	0.926	-0.002	0.998	0.789	1.262	0.986
$50,000 - $74,999	ref.	-	-	-	-	ref.	-	-	-	-
$75,000 - $99,999	-0.057	0.945	0.799	1.117	0.507	0.004	1.004	0.828	1.217	0.968
$100,000 - $124,999	0.049	1.050	0.870	1.267	0.613	0.061	1.063	0.856	1.320	0.580
$125,000+	-0.016	0.984	0.784	1.236	0.891	-0.005	0.995	0.766	1.293	0.971
Unknown/No SES information	0.099	1.104	0.905	1.346	0.332	0.135	1.144	0.910	1.439	0.250
Age of mother at infant date of birth										
<20	-0.499	0.607	0.087	4.231	0.614	-0.185	0.831	0.118	5.871	0.853
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.010	0.990	0.837	1.172	0.910	-0.031	0.969	0.801	1.173	0.748
35-39	0.039	1.039	0.854	1.265	0.700	-0.047	0.954	0.762	1.194	0.681
40-49	0.335	1.397	1.072	1.822	0.013	0.165	1.179	0.867	1.603	0.293
Multiple	0.130	1.139	0.903	1.436	0.273	0.114	1.121	0.860	1.462	0.399
Unknown Age Categorization	-0.114	0.892	0.567	1.404	0.623	-0.216	0.806	0.469	1.385	0.435
Age of father at infant date of birth										
<20	-0.347	0.707	0.110	4.537	0.714	0.041	1.041	0.162	6.676	0.966
20-29	ref.	-	-	-	-	ref.	-	-	-	-
30-34	-0.085	0.918	0.755	1.117	0.395	-0.039	0.962	0.764	1.211	0.742
35-39	0.040	1.040	0.841	1.287	0.715	0.177	1.193	0.931	1.530	0.163
40-49	0.158	1.171	0.928	1.477	0.183	0.303	1.354	1.035	1.772	0.027
Multiple	0.171	1.186	0.891	1.579	0.243	0.331	1.392	1.007	1.925	0.045
Unknown Age Categorization	-0.008	0.992	0.729	1.350	0.958	0.120	1.128	0.790	1.611	0.508
Mental health benefits[5]	0.097	1.102	0.927	1.310	0.270	0.014	1.014	0.833	1.234	0.893
Childhood Chronic Conditions Score (modified)[6]	0.232	1.261	1.182	1.346	<0.001	0.206	1.228	1.137	1.327	0.000
Seizures[7]	1.655	5.232	4.576	5.982	<0.001	1.743	5.713	4.904	6.654	0.000
Allergies[7]	0.493	1.637	1.116	2.403	0.012	0.478	1.612	1.033	2.517	0.035

Covariate	Outcome: Index Child ASD = Likely/Possible					Outcome: Index Child ASD = Likely				
	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value	Estimate	Hazards Ratio	Wald CI lower 95%	Wald CI upper 95%	p-value
Pre-term birth[7]	0.328	1.389	1.179	1.635	<0.001	0.295	1.343	1.111	1.623	0.002
Time/Age specific hazards ratios										
OLD SIB ASD=NO: One MMR dose at 1 years (365 days)	-0.047	0.954	0.677	1.343	0.787	-0.161	0.851	0.578	1.254	0.415
OLD SIB ASD=NO: One MMR dose at 2 years (731 days)	-0.025	0.975	0.759	1.253	0.845	-0.097	0.907	0.686	1.200	0.495
OLD SIB ASD=NO: One MMR dose at 3 years (1096 days)	-0.003	0.997	0.820	1.213	0.978	-0.034	0.967	0.777	1.204	0.764
OLD SIB ASD=NO: One MMR dose at 4 years (1461 days)	0.019	1.020	0.828	1.256	0.855	0.030	1.031	0.807	1.316	0.809
OLD SIB ASD=NO: One MMR dose at 5 years (1827 days)	0.042	1.043	0.788	1.380	0.771	0.094	1.099	0.785	1.538	0.583
OLD SIB ASD=NO: Two MMR doses at 3 years (1096 days)	-0.312	0.732	0.493	1.086	0.121	-0.427	0.652	0.414	1.029	0.066
OLD SIB ASD=NO: Two MMR doses at 4 years (1461 days)	-0.113	0.893	0.657	1.215	0.471	-0.159	0.853	0.593	1.227	0.391
OLD SIB ASD=NO: Two MMR doses at 5 years (1827 days)	0.087	1.091	0.813	1.463	0.564	0.109	1.115	0.782	1.590	0.547
OLD SIB ASD=LIKELY: One MMR dose at 1 years (365 days)	-0.223	0.800	0.498	1.286	0.358	-0.342	0.710	0.419	1.204	0.204
OLD SIB ASD=LIKELY: One MMR dose at 2 years (731 days)	-0.200	0.818	0.547	1.225	0.330	-0.278	0.757	0.485	1.182	0.220
OLD SIB ASD=LIKELY: One MMR dose at 3 years (1096 days)	-0.178	0.837	0.584	1.200	0.333	-0.215	0.807	0.542	1.202	0.292
OLD SIB ASD=LIKELY: One MMR dose at 4 years (1461 days)	-0.156	0.856	0.599	1.222	0.392	-0.151	0.860	0.575	1.286	0.462
OLD SIB ASD=LIKELY: One MMR dose at 5 years (1827 days)	-0.134	0.875	0.591	1.296	0.505	-0.087	0.917	0.582	1.443	0.708
OLD SIB ASD=LIKELY: Two MMR doses at 3 years (1096 days)	-1.047	0.351	0.200	0.617	0.000	-1.118	0.327	0.171	0.626	0.001
OLD SIB ASD=LIKELY: Two MMR doses at 4 years (1461 days)	-0.847	0.429	0.258	0.711	0.001	-0.851	0.427	0.237	0.771	0.005
OLD SIB ASD=LIKELY: Two MMR doses at 5 years (1827 days)	-0.648	0.523	0.318	0.860	0.011	-0.582	0.559	0.311	1.005	0.052

[1] N=96,054 likely/possible/no ASD index children with likely/no older sibling ASD; N=95,727 likely/no ASD index children with likely/no older sibling ASD.
[2] N=1,321 likely/possible/no ASD index children; N=994 likely/no ASD index children.
[3] MMR vaccination doses captured after year 1 birthday.
[4] Highest level among all mothers/fathers.
[5] Continuously enrolled with mental health benefits from birth to at least 60 months of age.
[6] Captured between birth and 24 months of age.
[7] Captured during each index child's entire enrollment period.