Importance
In recent years, rates of vaccination have been declining. Whether this phenomenon disproportionately affects children with autism spectrum disorder (ASD) or their younger siblings is unknown.

Objectives
To investigate if children after receiving an ASD diagnosis obtain their remaining scheduled vaccines according to the Advisory Committee on Immunization Practices (ACIP) recommendations and to compare the vaccination patterns of younger siblings of children with ASD with the vaccination patterns of younger siblings of children without ASD.

Design, Setting, and Participants
This investigation was a retrospective matched cohort study. The setting was 6 integrated health care delivery systems across the United States within the Vaccine Safety Datalink. Participants were children born between January 1, 1995, and September 30, 2010, and their younger siblings born between January 1, 1997, and September 30, 2014. The end of follow-up was September 30, 2015.

Exposures
Recommended childhood vaccines between ages 1 month and 12 years.

Main Outcome and Measure
The proportion of children who received all of their vaccine doses according to ACIP recommendations.

Results
The study included 3729 children with ASD (676 [18.1%] female), 592,907 children without ASD, and their respective younger siblings. Among children without ASD, 250,193 (42.2%) were female. For vaccines recommended between ages 4 and 6 years, children with ASD were significantly less likely to be fully vaccinated compared with children without ASD (adjusted rate ratio, 0.87; 95% CI, 0.85-0.88). Within each age category, vaccination rates were significantly lower among younger siblings of children with ASD compared with younger siblings of children without ASD. The adjusted rate ratios varied from 0.86 for siblings younger than 1 year to 0.96 for those 11 to 12 years old. Parents who had a child with ASD were more likely to refuse at least 1 recommended vaccine for that child's younger sibling and to limit the number of vaccines administered during the younger sibling’s first year of life.

Conclusions and Relevance
Children with ASD and their younger siblings were undervaccinated compared with the general population. The results of this study suggest that children with ASD and their younger siblings are at increased risk of vaccine-preventable diseases.
Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in communication and social interaction and the exhibiting of stereotyped behaviors, typically occurring before age 3 years. The etiology of ASD is unknown for the vast majority of cases; however, study findings suggest that both genetic and environmental factors have a role.

Despite numerous scientific studies reporting no association between childhood vaccination and ASD, there remain concerns about such a connection for some of the public. In recent years, rates of undervaccination and vaccine refusal have been on the rise in the United States and have been associated with vaccine-preventable disease outbreaks. Rates of undervaccination among the subpopulation of children with ASD have not been fully investigated. A survey conducted among 98 parents of children with ASD and 65 parents of children without ASD in Canada found that a lower proportion of children with ASD received their measles, mumps, and rubella (MMR) or diphtheria and tetanus toxoids and acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccines compared with children without ASD. Because the first dose of MMR and the first 3 doses of DTaP-IPV are recommended before the age when ASD can be reliably diagnosed (which is at least 2 years), it was not clear from that study if the lower observed vaccination rates among the children with ASD were a consequence of the child’s ASD diagnosis. In a recent letter to the editor, Glickman and colleagues reported no significant difference between rates of vaccination of 71 children with ASD and those of 135 children without ASD. However, they found that families with children with ASD were less likely to vaccinate subsequent children. Other studies also found that parents of children with ASD were more likely to either delay or refuse vaccination for their younger children. In a survey of 197 parents, Bazzano and colleagues found that half of the parents of children with ASD changed vaccination practices for their younger children because of beliefs that vaccines contributed to their child’s ASD. After surveying 486 parents of children with ASD, Rosenberg and colleagues found that almost 20% of parents declined or delayed MMR immunization in the younger siblings of children with ASD. Previous studies were limited by small samples, lack of comparable control groups, or restriction to specific vaccines.

The objectives of this study were 2-fold. First, we investigated if children after receiving an ASD diagnosis obtain all of their remaining scheduled vaccines according to the Advisory Committee on Immunization Practices (ACIP) recommendations. Second, we assessed whether younger siblings of children with ASD receive all recommended vaccines on time compared with younger siblings of children without ASD.

Methods

Study Population
The study population included children born between January 1, 1995, and September 30, 2010, and their younger siblings born between January 1, 1997, and September 30, 2014, who were members of integrated health care delivery systems (sites) within the Vaccine Safety Datalink (VSD). The VSD is a collaborative project between the Centers for Disease Control and Prevention and 8 sites across the United States and captures comprehensive medical and immunization data for more than 10 million people annually. This study included data from the following 6 VSD sites: Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Northwest, Kaiser Permanente Washington, Marshfield Clinic, and Kaiser Permanente Southern California. The study was approved by the institutional review board at each participating VSD site and the Centers for Disease Control and Prevention. Written informed consent was waived by each institutional review board because the study had no direct contact with patients.

Study Design
In this retrospective matched cohort study, we compared the proportion of vaccination between children with ASD and those without ASD. We also compared the proportion of vaccination of the younger siblings of children with ASD with those of the younger siblings of children without ASD.

Autism Spectrum Disorder
We defined ASD based on the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 299.0, 299.8, and 299.9 in electronic health records on at least 2 occasions from birth until either the sixth birthday or until the end of follow-up (September 30, 2015), whichever was earlier. If the first diagnosis appeared before age 2 years, we required that the second diagnosis be assigned at 2 years or older. A prior medical record review study demonstrated that identifying ASD using at least 2 diagnosis codes predicts valid ASD cases. We matched children without ASD to children with ASD on month and year of birth, sex, and VSD site. Younger siblings of children without ASD were matched to younger siblings of children with ASD on month and year of birth, sex, and VSD site. It is possible that multiple siblings of an individual with or without ASD were included because we did not limit the number of children per family.

Vaccination Status
To assess the vaccination patterns of children after receiving an ASD diagnosis, we only included children who were at least...
results

The study included 3729 children with ASD (676 [18.1%] female), 592 907 children without ASD, and their respective younger siblings. Among the children without ASD, 250 193 (42.2%) were female.

Vaccination Patterns in Children With and Without ASD

For vaccines recommended between ages 4 and 6 years, our analysis included 2855 children with ASD diagnosed by age 5 years matched to 483 961 children without ASD. The proportion of children who received all recommended vaccine doses (Table 1) between ages 4 and 6 years was lower in children with ASD compared with children without ASD (81.6% [2331 of 2855] vs 94.1% [455 435 of 483 961], respectively) (Table 2). The proportion receiving each individual vaccine was also lower among children with ASD compared with children without ASD. For MMR vaccine, 84.0% (2397 of 2855) of those aged 4 to 6 years with ASD were vaccinated compared with 95.9% (464 245 of 483 961) of those without ASD. After adjusting for maternal age at the time of the child’s birth and race/ethnicity (which were both associated with ASD in our bivariate analyses) and the matching variables (month and year of birth, sex, and site), children with ASD were significantly less likely to be fully vaccinated (adjusted RR, 0.87; 95% CI, 0.85-0.88) compared with children without ASD. Adjusted RRs were also significant for each individual vaccine.

For vaccines recommended at ages 11 to 12 years, the analysis included 874 children with ASD matched to 218 181 children without ASD. In this age group, the proportions receiving all vaccines (Table 1) and each individual vaccine were similar between children with ASD and children without ASD, and adjusted RRs were not significant (Table 2).

Table 1. On-Time Recommended Vaccine Doses by Age Group

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. of Doses by Age Group</th>
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<tbody>
<tr>
<td></td>
<td>1-11 mo</td>
</tr>
<tr>
<td>DTaP</td>
<td>≥3</td>
</tr>
<tr>
<td>HBV</td>
<td>≥2</td>
</tr>
<tr>
<td>Hib</td>
<td>≥2</td>
</tr>
<tr>
<td>HPV</td>
<td>NA</td>
</tr>
<tr>
<td>IPV</td>
<td>≥3</td>
</tr>
<tr>
<td>MCV4</td>
<td>NA</td>
</tr>
<tr>
<td>MMR</td>
<td>NA</td>
</tr>
<tr>
<td>PCV</td>
<td>≥3</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>≥2</td>
</tr>
<tr>
<td>Tdap</td>
<td>NA</td>
</tr>
<tr>
<td>VAR</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: DTaP, diphtheria and tetanus toxoids and acellular pertussis; HBV, hepatitis B virus; Hib, Haemophilus influenzae type b; HPV, human papillomavirus; IPV, inactivated poliovirus; MCV4, quadrivalent meningococcal conjugate; MMR, measles, mumps, and rubella; NA, not applicable; PCV, pneumococcal conjugate vaccine; Tdap, tetanus, diphtheria, and acellular pertussis; VAR, varicella vaccine.

*The Advisory Committee on Immunization Practices recommends 2 or more doses instead of 3 or more doses because the birth dose is included 2 or more shots per visit or shot limiting in the child’s first year of life, as well as the proportion of parents (based on ICD-9-CM codes) who refused to vaccinate their children. We calculated crude and adjusted rate ratios (RRs) using log binomial regression analysis. Because full vaccination is more common than undervaccination, the odds ratio for fully vaccinated would not be a good estimation of the RR. Therefore, we estimated the RRs by using proc GENMOD in SAS (version 9.3; SAS Institute Inc), with the log function as the link with binomial distribution. In multivariable analyses, we included maternal age categories at the child’s time of birth (≤20, 21-29, 30-39, or ≥40 years), maternal self-reported race/ethnicity (Asian, black, white, Hawaiian, Hispanic, Native American, or other), child’s sex, and month and year of birth. We used SAS version 9.3 to conduct all analyses. All P values were 2 sided, and P < .05 was considered statistically significant.
Vaccination Patterns in Younger Siblings of Children With and Without ASD

Within each age group, the proportion of children who were fully vaccinated with the recommended vaccines was lower among younger siblings of children with ASD compared with younger siblings of children without ASD. The difference in proportion of fully vaccinated children was greatest in the group aged 1 to 11 months (Table 3). The proportion of children who received each individual vaccine was lower for younger siblings of children with ASD compared with younger siblings of those without ASD within each age group. After adjusting for covariates, younger siblings of children with ASD were significantly less likely to be fully vaccinated than were younger siblings of children without ASD within each age group, except for vaccines recommended between ages 11 and 12 years. Rate ratios of undervaccination comparing younger siblings of children with ASD and those without ASD were lowest in the groups aged 1 to 11 months and 1 to 2 years.

A higher proportion of parents of children with ASD refused to vaccinate their younger children compared with parents of children without ASD (Figure). These parents were also more likely to limit the number of vaccines administered during well-child visits in the group aged 1 to 11 months (73 of 881 [8.3%] for younger siblings of children with ASD vs 2789 of 189144 [1.5%] among younger siblings of children without ASD, P < .001). For both ASD cases and their siblings, we found no significant differences in the RR of undervaccination over time (eTable in the Supplement).

Discussion

In this large multisite study, we found that vaccine uptake was high overall. However, after receiving an ASD diagnosis, children with ASD were subsequently less likely to be vaccinated compared with children without ASD matched on age, sex, and site. We also found that vaccination rates were lower among younger siblings of children with ASD compared with younger siblings of children without ASD. Parents of children with ASD were more likely to refuse vaccinating the children’s younger siblings compared with parents of children without ASD. This phenomenon was not observed for vaccines recommended at ages 11 to 12 years for children with ASD and their younger siblings.

Our results are similar to those of a Canadian study,25 which reported that children with ASD and their younger siblings were undervaccinated for MMR and pertussis-containing vaccines compared with children without ASD. However, there are major differences between our study and the Canadian study, including our larger sample size and more targeted study design. In our comparison of vaccination status between children with ASD and those without ASD, we only assessed vaccines recommended after the child’s ASD diagnosis, which enables the inference that the lower vaccination rate in children with ASD was at least in part owing to the ASD diagnosis.

In the present study, within each recommended age category of vaccination before age 10 years, younger siblings of children with ASD were significantly more likely to be undervaccinated compared with younger siblings of children without ASD, suggesting that the ASD diagnosis of the older sibling may have contributed to the undervaccination of the younger children. Knowing that younger siblings of children with ASD are at higher risk for ASD34-37 may have led some parents of children with ASD to either delay or refuse vaccinations for the younger siblings. It is also possible that health care professionals may have been more likely to assign the code for vaccine refusal for the siblings of children with ASD when they know that the family has a child with ASD. Parents of children with ASD may also delay or alter the vaccination schedule of...
their younger children because of concerns that vaccines may have had a role in causing the ASD of the older siblings; this is despite considerable scientific evidence that vaccines do not cause autism. As previously reported, most parents vaccinate their children according to the ACIP-recommended schedule. However, an increasing number of parents, especially parents of children with ASD, also appear to limit the number of vaccines their children receive during their child’s first year of life; the safety of such alternative vaccination schedules is unknown, but this practice increases the chances for contracting a vaccine-preventable disease.

The highest rates of undervaccination in this study were among siblings of children with ASD who were in the groups aged 1 to 11 months and 1 to 2 years. This suggests that some parents consider the potential risks of ASD associated with vaccination to be greatest at these younger ages at which more vaccines are recommended. However, as these children grow older, these parents may be more willing to vaccinate.

Limitations and Strengths
Our study has some limitations. Autism spectrum disorder status was determined using specific diagnostic codes from automated data, and medical record reviews were not conducted. However, our case definition, which required at least 2 codes for ASD on different days, has been shown to identify true cases of ASD with high accuracy. Although the overall
sample size of the study was large, the analysis comparing vaccination status of the younger siblings for the group aged 11 to 12 years was small, which limited the validity and power to observe differences in vaccine patterns in this group. We required that children in the study be a health plan member during the periods we assessed their vaccination status; while it is possible that some children may have received some of their vaccines outside of the VSD sites, this is considered unlikely because vaccines are offered free of charge at all of the participating sites. For missing vaccine doses to affect our results, the data missing would have to be differential for families with and without children with ASD. Our rates of under-vaccination among children with ASD may reflect an underestimation of the true rates because we did not assess vaccination status before the ASD diagnosis. We did not conduct medical record reviews to validate the codes for vaccine refusal. Rates of vaccine refusal in this study likely underestimate the true rates of vaccine refusal because vaccine refusal is not always coded in the medical record consistently by physicians. Our rates could be biased toward or away from the null value because we cannot determine if ASD status is always associated with better or worse documentation of vaccine refusal. For some vaccines, different numbers of doses are recommended depending on which vaccine is used; we did not examine specific vaccine formulations. We were not able to assess the birth dose of hepatitis B vaccine because not all children included in our study were born at the health care organizations included in the study. Finally, we cannot attribute all of the undervaccination findings for the younger siblings of children with ASD to the ASD diagnosis of the older sibling because it is possible that some parents may have modified their younger children’s vaccine schedule without knowing the ASD status of the older children or for other reasons, including health care professional recommendations or some unknown factors.

This study’s strengths include our large racially/ethnically and socioeconomically diverse population from 6 different geographic areas, suggesting that the findings may be broadly generalizable to other populations. We also used vaccination data validated from the medical record instead of a parental report, which could be subject to recall bias or incomplete information. Furthermore, we had extensive vaccination data over many years and were thus able to assess the vaccination rate for recommended childhood vaccines between ages 1 month and 12 years for the younger siblings of children with ASD. In addition, we were able to match a large comparison group with the children with ASD and identify the younger siblings of both children with and without ASD. By matching on month and year of birth, the study minimized the possibility of a difference in the interpregnancy interval between cases and controls or between siblings of cases and siblings of controls.

Conclusions

This large multisite study found that children with ASD and their younger siblings were undervaccinated compared with the general population, suggesting that they are at increased risk of vaccine-preventable diseases. Although we do not know all factors contributing to undervaccination among children with ASD, the results of our study suggest that parental vaccine refusal could have a role. Previous studies reported that a large proportion of parents of children with ASD consider that vaccines contributed to their child’s ASD, and consequently they either changed or discontinued vaccination, suggesting that current strategies to address vaccine hesitancy have not been effective for parents of children with ASD. New strategies, including establishing or promoting a better dialogue among parents, health care professionals, and public health authorities, may be needed to increase vaccine uptake in populations with low uptake.

References

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Vaccination Patterns in Children After Autism Spectrum Disorder Diagnosis and in Their Younger Siblings


