

Time Trends in Autism and in MMR Immunization Coverage in California

Loring Dales, MD

Sandra Jo Hammer, RN, PHN

Natalie J. Smith, MD, MPH

IN THE MID TO LATE 1990S, A MEDICAL investigative group in Great Britain postulated that measles immunization and/or immunization with measles, mumps, and rubella vaccines given combined at the same time or in succession over a relatively short time period might be a cause of the developmental disorder autism.¹ Strong interest in and debate over this hypothesis has occurred. In this connection, some cite a 1999 report from the California Department of Developmental Services² showing an increase within the past 2 decades in its regional system caseload of children with autism, wondering if increasingly widespread combined measles-mumps-rubella (MMR) immunization of young children might have been responsible for this increase.³ Also, multiple news media stories and Internet Web site presentations on MMR vaccine and autism have cited these California autism data.^{4,5}

Autism, an incompletely understood developmental disorder or group of related disorders, varies in clinical presentation, so diagnosis is not always straightforward. Further, temporal associations between receipt of MMR vaccine and autism onset can occur by chance alone, since MMR vaccine is typically given at 12 to 15 months of age, and the median age at which parents of children with autism first notice troubling signs in their children's development is approximately 18 to 19 months of age.⁶

The aforementioned California Department of Developmental Services report stresses that its patient caseload

Context Considerable concern has been generated in the lay and medical communities by a theory that increased measles-mumps-rubella (MMR) immunization among young children may be the cause of an apparent marked increase in autism occurrence.

Objective To determine if a correlation exists in secular trends of MMR immunization coverage among young children and autism occurrence.

Design, Setting, and Participants Retrospective analyses of MMR immunization coverage rates among children born in 1980-1994 who were enrolled in California kindergartens (survey samples of 600-1900 children each year) and whose school immunization records were reviewed to retrospectively determine the age at which they first received MMR immunization; and of autism caseloads among children born in these years who were diagnosed with autism and were enrolled in the California Department of Developmental Services regional service center system.

Main Outcome Measures Measles-mumps-rubella immunization coverage rates as of ages 17 months and 24 months and numbers of Department of Developmental Services system enrollees diagnosed with autism, grouped by year of birth.

Results Essentially no correlation was observed between the secular trend of early childhood MMR immunization rates in California and the secular trend in numbers of children with autism enrolled in California's regional service center system. For the 1980-1994 birth cohorts, a marked, sustained increase in autism case numbers was noted, from 44 cases per 100 000 live births in the 1980 cohort to 208 cases per 100 000 live births in the 1994 cohort (a 373% relative increase), but changes in early childhood MMR immunization coverage over the same time period were much smaller and of shorter duration. Immunization coverage by the age of 24 months increased from 72% to 82%, a relative increase of only 14%, over the same time period.

Conclusions These data do not suggest an association between MMR immunization among young children and an increase in autism occurrence.

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data cannot be used as a true measure of changes over time in autism incidence because other factors can affect trends in system case numbers.² Further, "ecological correlations," that is, observations of parallel trends over time or across geographic locations for 2 events, generally do not constitute strong evidence for a causal association between the 2 events.⁷ Other events besides a possible increase in early childhood immunization with MMR vaccine have occurred over the time period of the increase in autism cases.

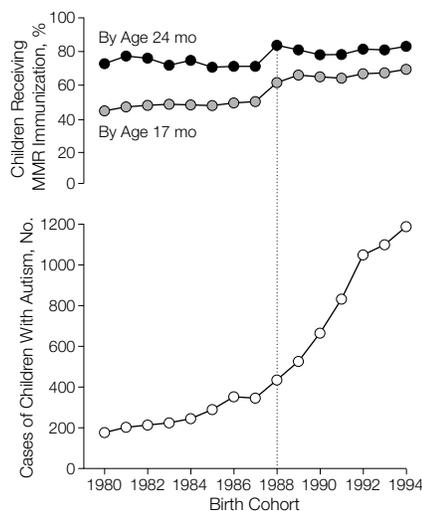
Nonetheless, given concerns expressed about this matter, we have ex-

amined California data on early childhood MMR immunization levels over time along with the data on autism caseloads during the same period. The combined MMR vaccine was licensed for use in the United States in 1971, and over the remainder of the 1970s, almost completely replaced use of the individual measles, mumps, and rubella vaccines for routine immunization of young children. Since 1979, the MMR

Author Affiliations: Immunization Branch, California Department of Health Services, Berkeley.

Corresponding Author and Reprints: Loring Dales, MD, Immunization Branch, California Department of Health Services, 2151 Berkeley Way, Room 712, Berkeley, CA 94704 (e-mail: ldales@dhs.ca.gov).

Figure. Percentage of Children Receiving Measles-Mumps-Rubella (MMR) Immunization in Second Year of Life and Caseload of Children With Autism, by Year of Birth, California, 1980-1994



The upper 2 curves indicate the percentages of children receiving MMR immunization by 17 and 24 months of age, respectively. The lower curve indicates the number of cases of children with autism² (and California Department of Development Services, unpublished data, 2000). The vertical dotted line at birth year 1988 is provided as a temporal reference point in comparing the shapes of these curves.

preparation used in the United States has not changed in composition. Thus, for children born in California from 1980 onward, the secular trend in the proportion of children who received MMR immunization at an early age is the logical parameter to compare with the apparent trend of increasing autism occurrence.

METHODS

Since the early 1970s, the California Department of Developmental Services has funded a system of regional centers for persons with developmental disabilities, including autism. These regional centers, now 21 in number and covering all of the state's 58 counties, function as service hubs, coordinating, linking, and funding services for eligible persons. The 1999 report on trends in the system's autism caseload compiled demographic and patient developmental evaluation record data electronically submitted to the department

by the 21 regional centers.² Because the increase in this system's autism caseload occurred within the past 2 decades, we examined the data for children born between 1980 and 1994, the latter being the latest patient birth year for which a relatively complete system autism caseload count is currently available. The California Department of Developmental Services supplied caseload numbers for the diagnostic category "autistic disorder" (*International Classification of Diseases, 9th Edition*, code 299.00), which excludes other pervasive developmental disorders.

The early childhood MMR immunization level estimates for California children by year of birth come from the California Department of Health Services annual surveys of statewide random samples of public and private school kindergarten pupils' immunization records. The number of children included in the surveys' random samples selected each year increased from approximately 600 to 800 children born each year in 1980 through 1984 to between 1000 and 1900 annually for children born in 1985 through 1994, but otherwise the sampling method remained virtually the same throughout the whole time period. School immunization records of the kindergarten children sampled, who were 5 to 6 years of age at the time of the surveys, were assessed retrospectively to determine at what earlier ages they received their immunizations. Per standard national recommendations extant over this time period, children should have received their initial MMR immunization at 12 to 15 months of age. Two immunization coverage measures are presented here: the proportions of children in each year's survey sample who had received MMR immunization by the age of 17 months, and the proportions that had received such immunization by the age of 24 months. Immunization coverage by the age of 17 months is presented because this age just precedes the median age when parents of children with autism first note signs of developmental problems. Immunization coverage through the age

of 24 months is presented to detect a potential secular trend on increasing vaccine coverage that might have been missed when the 17-month age checkpoint was used.

RESULTS

The upper 2 curves in the FIGURE show the percentages of children who received MMR immunization by the age of 17 months and by the age of 24 months (including children immunized by 17 months of age), by birth year, for each annual California kindergarten retrospective immunization survey sample cohort, for birth years 1980 through 1994. As can be seen from the 2 upper curves, for the 1980 through 1987 birth year cohorts, there was almost no change in MMR coverage. A modest increase occurred with the 1988 birth cohort, followed again by a near plateau with little change in coverage over the next 6 years, through the 1994 birth cohort. The relative increase in MMR coverage by age 24 months from birth year 1980 to 1994 was 14%, from 72% to 82%.

The lower curve in the Figure shows a major trend of increase in autistic disorder cases beginning with the 1985 birth year cohort (and possibly even earlier), well before the MMR coverage increase that occurred with the 1988 birth cohort. Further, this trend of autistic disorder caseload increase continues at least through the 1994 birth cohort. Thus, the trend of increasing autism caseload numbers persisted long after the MMR immunization coverage curve leveled off again with the 1988 birth cohort.

The trend of increasing numbers of autistic disorder cases, from 176 cases for birth year 1980 to 1182 cases for birth year 1994 (a relative increase of 572%), is many times greater in relative magnitude than the modest increase observed for MMR coverage. If the autistic disorder case data are computed as rates, using annual numbers of births in California as denominators, the increase noted for the lower curve in the Figure is only slightly less pronounced, increasing from 44 per

100 000 births for the 1980 birth cohort to 208 per 100 000 births for the 1994 birth cohort, representing a 373% relative increase.

COMMENT

The lack of correspondence between the trends in MMR coverage and numbers of autistic disorder cases does not support the hypothesis that increasingly widespread MMR immunization of young children is associated with the marked secular trend of increasing numbers of autism cases enrolled in the California Department of Developmental Services regional service center system. Difficulties in interpreting the increasing numbers of autism cases are highlighted in the California Department of Developmental Services 1999 report, which repeatedly stressed that its data cannot be interpreted as measuring trends in the actual incidence of autism.² It is unknown how many children with autism have not enrolled in the system and, as the system expanded and matured over time, the proportions of California children enrolling and the distribution of ages at enrollment likely changed over time as a result. Also, the proportions of children enrolling in the system who were born outside California may have changed over this time period. In addition, diagnostic methods and categorizations of persons with autism have changed over time. Recommendations have been made for a detailed investigation into the apparent secular increase in autism cases, carefully evaluating the extent to which apparent increases in autism are real as op-

posed to artifact, as well as evaluating factors that may have contributed to any true increases including immunizations.^{2,8} Such investigations are in progress (Robert Byrd, MD, University of California Davis Medical Center, Department of Pediatrics, written communication, November 1, 2000).

However, the issue here is, assuming that the secular trend noted in the report represents a true increase in autistic disorder incidence, what is the evidence that MMR immunization may be associated with this trend? That is, does an ecological correlation exist between MMR immunization coverage rates of young children and the system's autism caseload? If MMR immunization of young children was associated with a secular trend in autism incidence, one would expect a curve for the numbers of autism cases among the 1980-1994 birth year cohorts that is very similar to the shapes of the curves for temporal trends in MMR coverage. That is, the numbers of cases should be rather stable for the 1980-1987 cohorts, followed by a small increase and then more or less a plateau at a new, modestly higher level for the 1988-1994 birth cohorts. As can be seen from the lower curve in the Figure, however, this is not the case.

The data presented herein have some limitations. It would have been useful to examine individual immunization and autism records on the same children; however, these could not be linked. Further, the childhood immunization coverage data used in this study do not provide precise quantification of the percentages of children who re-

ceived the combined MMR vaccine product vs separate injections of the measles, mumps, and/or rubella components. However, the historical information on MMR vaccine usage in the United States, as well as information in the immunization coverage data set itself, strongly suggest that separate injections of measles, mumps and/or rubella vaccines to young children were rare during the time period under consideration, particularly for the 1984-1994 birth cohorts, in which the trend of increase in the system's autistic disorder caseload is most pronounced.

Thus, examination of available data from California has been unable to demonstrate a correlation between secular trends in early childhood MMR immunization coverage and autism caseload levels. A similar lack of correlation between the trends in early childhood MMR immunization rates and autism occurrence has been noted in Great Britain⁶ and Sweden.⁹ In conclusion, to date, published observations based on empirical evidence do not suggest that increased MMR immunization among young children is associated with secular increases in cases of autism.

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Acquisition of data: Dales.

Analysis and interpretation of data: Dales, Hammer, Smith.

Drafting of the manuscript: Dales.

Critical revision of the manuscript for important intellectual content: Dales, Hammer, Smith.

Statistical expertise: Dales, Smith.

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Study supervision: Dales, Smith.

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