

Autism and Vaccination—The Current Evidence

Lisa Miller, MD, MSPH and Joni Reynolds, RN, MSN

PURPOSE. *The purpose of this article is to review relevant background literature regarding the evidence linking thimerosal-containing vaccine and the measles, mumps, and rubella vaccine to autism.*

CONCLUSIONS. *Rigorous scientific studies have not identified links between autism and either thimerosal-containing vaccine or the measles, mumps, and rubella vaccine.*

PRACTICE IMPLICATIONS. *Nurses are often in the position of providing advice regarding vaccines in their formal practice areas as well as in their daily lives. Families need current and credible evidence to make decisions for their children. Excellent vaccine information resources are available online.*

Search terms: *ASD, autism, immunization, MMR, measles, thimerosal, vaccine*

Lisa Miller, MD, MSPH, is the Disease Control and Environmental Epidemiology Division Director, and Joni Reynolds, RN, MSN, is the Immunization Program Director, Colorado Department of Public Health and Environment, Denver, Colorado, USA.

Autism Spectrum Disorders (ASD) are a group of developmental disabilities characterized by impairments in social interaction and communication and repetitive behaviors. The prevalence of these conditions has increased over the past several decades, but it is unclear whether this is due to a true increase, increasing awareness, or differences in the methods used to assess prevalence. By definition, the onset of ASD occurs prior to age 3 (Volkmar & Pauls, 2003).

No clear etiology has been identified for ASD, although many possible associations have been investigated (Newschaffer et al., 2007). Given the increase in prevalence, there has been interest in “environmental” exposures that may have also increased over the past several decades. One of these exposures, vaccinations, has received widespread interest and attention. An increasing number of vaccinations have become available over the past several decades to protect children against infectious diseases, and many are given at a time period during early childhood that coincides with the onset of developmental concerns related to autism.

This article will explore vaccination history, vaccine safety monitoring systems in the United States, and the two most publicized theoretical vaccine-related exposures that have been associated with autism—the vaccine preservative thimerosal and the measles, mumps, and rubella (MMR) vaccine. Understanding both the history and recent research will assist nurses in providing accurate patient information and in interpreting new findings in an area that continues to generate controversy and research interest.

The art and science of vaccinology is complex and requires significant rigor in educating providers about vaccines and their administration. Vaccines are a cornerstone in public health practice, as “Vaccines are one of the greatest achievements of biomedical science and public health” (Centers for Disease Control and Prevention [CDC], 1999a, p. 247). Yet, the success of vaccines and drastically reduced rates of disease have resulted in parents not experiencing firsthand the significant effects of these diseases. Some parents are

First Received November 14, 2008; Revision received February 25, 2009; Accepted for publication March 16, 2009.

now more concerned about the risks, real and theoretical, of recommended childhood vaccines.

History of Vaccines

The earliest medical vaccine is considered to be the smallpox vaccination, developed by Dr. Edward Jenner in the eighteenth century. Impressively, Jenner's work preceded the work of Louis Pasteur, who introduced the concept of viruses to the scientific world.

In 1796, Edward Jenner vaccinated James Phipps using material from a cowpox lesion on the hand of a milkmaid, theorizing that vaccination with cowpox would lead to immunity against the dreaded smallpox. A later attempt to give Phipps smallpox demonstrated his immunity, and the vaccination era began. Although Jenner lacked our understanding of viruses, the immune system, or vaccinology, his clinical observations convinced him that milkmaids were protected from smallpox because of their previous exposure to cowpox, and he acted to see if nature could be replicated (Foege, 2006).

Of the many illnesses circulating in the twentieth century, none was as widely feared as polio, which caused crippling illness, particularly in children. There were many pools and beaches closed in the summertime due to concerns of polio epidemic. Parents feared polio and anxiously supported the development of a polio vaccine.

Dr. Salk introduced the first killed polio vaccine in the United States in 1955 through massive clinical trials. There were concerns with the vaccine, however, as several hundred cases of paralytic polio were induced by the vaccine. Dr. Sabin researched and developed a different polio vaccine that was introduced in the early 1960s. This vaccine proved to be safer than and as effective as the prior polio vaccine. An improved Salk Inactivated Polio vaccine is still used routinely for U.S. children today, while the Sabin Oral Polio vaccine is used in some international efforts to eradicate polio worldwide.

These early vaccine pioneers were fortunate to have success. Historically, it was a common trait among scientists to take personal risks for the benefit of science. Jenner, Salk, and Sabin risked their reputations for these early breakthroughs, setting the stage for future vaccine development. Today, the risks and benefits of vaccines are closely calculated and monitored. The early vaccines were developed using a crude approach compared to the laboratory-based vaccine development processes of today.

Vaccines Today

Today there are routine vaccines that can protect individuals from measles, mumps, rubella, chickenpox, pertussis, diphtheria, tetanus, invasive *Haemophilus influenzae* type b (Hib) infections, viral hepatitis A, viral hepatitis B, invasive *Streptococcus pneumoniae* infections, influenza, human

papillomavirus, rotavirus, invasive meningococcal infections, and polio. In addition, there are vaccines that can protect high-risk individuals from other diseases, including smallpox, yellow fever, rabies, anthrax, Japanese encephalitis, herpes zoster (shingles), and typhoid fever.

The Advisory Committee on Immunization Practices (ACIP) provides recommendations for vaccinations to the CDC. Annually, the CDC, the American Academy of Pediatrics, and the American Academy of Family Physicians jointly publish a schedule of recommended immunizations. Children today are routinely vaccinated against 14 diseases during their infancy and preschool years.

Childhood vaccinations are administered as early as possible to assure that infants are protected against diseases that occur in early childhood. Some have questioned the need to administer vaccines according to the recommended ACIP schedule, essentially indicating it is too many vaccines too early for children (Ball et al., 2001). The timing of vaccines is essential to assure that, if possible, protection precedes the disease exposure. It's key to remember that literally from birth, infants are exposed to environmental organisms that can cause infections. Delaying vaccines can be risky because it extends the time that infants are susceptible to real diseases that can have serious complications, particularly for the youngest children.

The goal of the immune system is to identify "non-self" and destroy it. The basic components of the immune system include antigens (non-self foreign bodies) and antibodies (our defense against the antigens). Immune systems are exposed to hundreds or thousands of antigens daily. Infant immune systems are capable of responding to these routine exposures, which present themselves from the moment of birth. Infants and children build effective antibodies to vaccine antigens and are then able to develop internal defenses against a variety of infectious diseases, many of which took a tremendous toll in the past.

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Information Regarding Systems for Vaccine Safety Monitoring

Parents, nurses, other medical providers, vaccine manufacturers, and the government all play critical roles in monitoring the safety of vaccines. As parents know their children

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best, it is important to encourage them to trust their instincts related to their children's health. Parents should report any concerns after their children's vaccinations to their primary healthcare provider. Nurses and other healthcare providers are required to record key information (e.g., lot number, product, administration site, and method) for each vaccine administered, which can be used when reporting a possible vaccine adverse event. Vaccine lot numbers can be used to track unusual patterns within a specific vaccine lot. In addition, if necessary, a provider can identify which patients received a dose of recalled vaccine.

The National Childhood Vaccine Injury Act was passed in 1986. The Act created the National Vaccine Injury Compensation Program, which provides compensation for those found to be harmed by specific vaccines. This Act also requires healthcare providers to report any serious adverse events that occur within 30 days after vaccination with any vaccine. The reports must be submitted to the Vaccine Adverse Event Reporting System (VAERS), which was set up in 1990 and is managed by the CDC and the Food and Drug Administration (FDA). Reports can be submitted online at <http://vaers.hhs.gov/>. This is a passive surveillance system that accepts all submitted reports without validation. The VAERS can identify reporting trends that need further investigation. In 1999, the suspicion of a link between the rotavirus vaccine and intussusception was identified through the VAERS (Department of Health and Human Services, n.d.).

Vaccine manufacturers are required to complete prelicensing vaccine testing through clinical trials for each vaccine. In addition, vaccine manufacturers are required by the National Childhood Vaccine Injury Act to report adverse events to the Department of Health and Human Services (CDC, n.d.). Vaccine manufacturers have a vested interest in assuring vaccines are safe, reinforcing public confidence in vaccines.

The Vaccine Safety Datalink includes data from several health maintenance organizations. This database is used to monitor for any possible adverse event from vaccines. Large, ongoing studies are conducted using these data (CDC, n.d.).

The FDA monitors adverse events reporting rates, using both the VAERS data and manufacturer's data. Among the things the FDA looks for are large numbers of adverse event reports early in the circulation of a lot, clusters of similar cases, syndromes (groups of symptoms), or other patterns; additional information from other sources with knowledge of a particular case; patterns of reported adverse events linked to final lots filled from the same bulk vaccine; and documentation that lots in question have passed all the required tests.

Measles, Mumps, and Rubella (MMR) Vaccine

The MMR vaccine was licensed in the United States in 1971 and includes a live, attenuated measles strain. The

vaccine results in an asymptomatic or mild infection that cannot be transmitted to others. Measles vaccination has resulted in a decrease in reported measles cases from about 500,000 cases and 500 deaths per year to a few dozen cases each year in the United States (CDC, 2007). In 2008, however, more than 100 cases were reported, due to importations from other countries. Most of these cases have occurred among unvaccinated persons (CDC, 2008b). The ACIP recommends that MMR be administered between the ages of 12 and 15 months, with a second dose administered between 4 and 6 years of age (Kroger, Atkinson, Marcuse, & Pickering, 2006).

A decade ago, a British researcher and 12 coauthors published a paper describing abnormal gastrointestinal features among 12 children who had been referred to their university pediatric gastroenterology clinic. All children had some type of developmental disorder, and in 9 of the children, a diagnosis of autism had been made. In 6 of these 9 children, either the parent or a physician had linked the onset of developmental regression with the receipt of the MMR vaccine (Wakefield et al., 1998). In 2000, a second paper was published, in which white blood cells in the same 9 autistic children (with what was now referred to as "autistic enterocolitis") were examined for the presence of measles virus. Using polymerase chain reaction, the measles virus RNA fragments were found in 3 out of the 9 children but in none of the 22 controls (Kawashima et al., 2000). In 2004, 10 of the 11 coauthors of Wakefield's original paper asked to "formally retract the interpretation placed upon these findings..." (Murch et al., 2004).

However, these initial reports of a possible relationship between the MMR vaccine and the onset of autism received significant attention, and in England, MMR immunization rates dropped from greater than 90% prior to 1998 (National Statistics, T.I.C., 2005) to a low of 80% in 2003–2004 (National Statistics, T.I.C., 2008).

In response to this concern in the United States, the CDC and the National Institutes of Health convened a panel of experts in the fall of 2000 to examine three vaccine safety issues, the first of which was the hypothesis of a link between the MMR vaccine and autism (Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention, & Institute of Medicine, 2001). The committee, after performing an in-depth review of the relevant scientific and medical literature, rejected a causal relationship between the MMR vaccine and ASD based on the following: (i) a lack of epidemiologic evidence linking autism and MMR vaccine, (ii) case reports of children with autism and bowel disorders that did not address causality, and (iii) a lack of biologic models linking ASD and MMR vaccine. Similarly, the American Academy of Pediatrics and the Medical Research Council both published similar conclusions (Halsey & Hyman, 2001; Medical Research Council, 2001) in 2001, based on the research available at that time.

Shortly thereafter, several studies were published refuting the association between MMR vaccine and autism. One of the first examined the California Department of Developmental Services data and the state's MMR immunization rate data. They hypothesized that if there were a link, the pattern of change in the immunization rate should be similar to the pattern of change in the autism rate. Instead, they found that the autism rate had increased by 373% between 1980 and 1994 but the immunization rate had been fairly constant during that period, increasing by only 14% (Dales, Hammer, & Smith, 2001).

In that same year, another pair of British researchers set out to test several theories suggested by the hypothesis of a link between a regressive form of autism and the MMR vaccine. The researchers compared a group of children with autism who had been diagnosed prior to the introduction of the MMR vaccine with two groups of children with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS; a condition in which children have some of the features of autism) or autism diagnosed after the introduction of MMR vaccine. Among the theories tested was that the mean age of parental concern should be younger, or closer to the age at vaccination in the vaccinated group. Instead, there was no difference between groups. If MMR vaccine were associated with a regressive form of autism, the authors also theorized that the rate of regression would be higher in the groups of children who had received the vaccine. Such an association was not seen (Fombonne & Chakrabarti, 2001). Later, a group of U.S. researchers tested similar theories with a large group of well-studied children with autism. They also found no support for the hypothesis, though they did find a higher rate of gastrointestinal symptoms in children with autism and regression compared to children with autism but no regression. However, they also documented that for many of the children with regression, communication skills prior to the onset of regression was atypical (Richler et al., 2006).

Kaye, Mar Melero-Montes, and Jick (2001) examined the temporal trends by comparing rates of autism in England between boys born in 1988, when MMR vaccine was introduced, and those born in 1993. They found that while the rate of autism diagnoses increased almost fourfold, the rate of MMR immunization was fairly constant over that time period. The authors also compared the mean age at vaccination among those with an autism diagnosis to the mean age at vaccination among the general population and found no difference.

Madsen et al., in 2002, published findings from a cohort of more than half a million children in Denmark that found no difference in the risk of autism between MMR-vaccinated and unvaccinated children. Further evidence was provided in 2004 from a case control study in which the rate of MMR vaccination among children with PDD-NOS was compared to the rate

among those without PDD-NOS. The study concluded that those with PDD-NOS were no more likely to have been vaccinated than those without PDD-NOS (Smeeth et al., 2004).

In 2005, researchers reported on the incidence of autism in an area of Japan where MMR vaccination was withdrawn in 1993. They found that the incidence of autism continued to increase, even after the withdrawal (Honda, Shimizu, & Rutter, 2005). Fombonne, Zakarian, Bennett, Meng, and McLean-Heywood (2006) also examined the relationship of MMR vaccination rates with autism rates in Canada, noting that among children born from 1987 to 1998, PDD-NOS increased in a linear fashion, while MMR immunization rates just slightly increased. In addition, a second MMR was added for children at 18 months beginning with those born in 1996. This additional MMR dose did not affect the rate at which PDD-NOS increased (Fombonne et al.).

In addition to the epidemiologic reports examining the relationship between MMR vaccine and autism, others have tried to replicate the findings of measles virus RNA in children with autism. Three studies (Afzal et al., 2006; D'Souza, 2006; Baird et al., 2008) have found no difference in the prevalence of measles virus in peripheral blood mononuclear cells between children with autism and controls, or failed to find any virus in either group. Martin et al. (2002) did find measles virus RNA more commonly in the bowel tissue of children with autism and regression compared to a group of controls, using a variety of polymerase chain reaction methods. More recently, Hornig et al. (2008) have reported negative findings among 25 children with autism and 13 control children, all with clinically significant gastrointestinal symptoms. No significant difference in the prevalence of measles virus RNA in bowel tissue was found between the cases (4%) and controls (8%).

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As the preponderance of evidence from around the world has accumulated showing no relationship between MMR vaccine and autism, MMR immunization rates in England have begun to increase. In 2007–2008, rates were 85%, up from their low of 80% (National Statistics, T.I.C., 2008). However, measles cases have increased dramatically in England, from only 56 cases in 1998 to 1,370 cases in 2008 (Health Protection Agency, 2008). Interestingly, in the United States, national immunization rates for MMR vaccine have not dipped below

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90% since 1995, and they have showed no significant reduction during the controversy (CDC, 2001, 2004, 2008a).

Thimerosal

Vaccine manufacturers who produce multidose vaccine vials use thimerosal as a preservative. Thimerosal is approximately 50% mercury by weight, and it has been one of the most widely used preservatives in vaccines. It is metabolized or degraded to ethylmercury and thiosalicylate. Ethylmercury is an organomercurial that should be distinguished from methylmercury, a related substance that has been the focus of considerable study (Thimerosal in Vaccines, n.d.). Methylmercury is bioavailable and can accumulate in the brain and cause neurologic damage. The ethylmercury found in thimerosal is not bioavailable. In studies, ethylmercury does not accumulate in the body or the brain and is metabolized and cleared by the body (Burbacher, Shen, Liberato, Grant, & Cernichiari, 2005).

Thimerosal has antimicrobial qualities that keep vaccines safe from inadvertent contamination through routine multiple punctures in a vial. Thimerosal had been used by vaccine manufacturers for years but came under scrutiny in 1999, as discussed earlier in this article. At that time, the FDA and the CDC published statements that indicated manufacturers should reduce or eliminate the amount of thimerosal used in vaccines. The CDC further recommended the birth dose of hepatitis B vaccine be suspended for infants until thimerosal-free vaccine was available (CDC, 1999b).

The CDC stated:

... given the widely acknowledged value of reducing exposure to mercury, vaccine manufacturers, the FDA, and other Public Health Service (PHS) agencies are collaborating to reduce the thimerosal content of vaccines or to replace them with formulations that do not contain thimerosal as a preservative as soon as possible without causing unnecessary disruptions in the vaccination system. The FDA will expedite review of supplements to manufacturers' product license applications that present formulations for eliminating or reducing the mercury content of vaccines. (CDC, 1999, p. 997)

Vaccine manufacturers then worked to assure removal of thimerosal from vaccines. By 2001, all vaccines routinely recommended for children 6 years of age and under in the United States were produced without thimerosal as a preservative, with the exception of some doses of inactivated influenza vaccine. Today, all vaccines are available without thimerosal, including several influenza vaccine presentations (e.g., single-dose prefilled syringes and the intranasal vaccine).

Many studies have been undertaken to examine the risks associated with thimerosal in vaccines. In 2003, Stehr-Green et al. assessed autism incidence and the use of thimerosal-containing vaccines: "Data did not support an association between thimerosal-containing vaccines and autism in Denmark and Sweden where exposure to thimerosal was eliminated in 1992 and where autism rates continued to increase" (Stehr-Green et al., 2003, p. 106).

Another study in 2003 utilized the Vaccine Safety Datalink (VSD) to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of renal, neurologic, and developmental problems: "No consistent significant associations were found between thimerosal-containing vaccines and neurodevelopmental outcomes" (Verstraeten et al., 2003, p. 1,042).

The CDC conducted a follow-up study to the Verstraeten et al. VSD study. This was a large study that also utilized the VSD data to investigate a possible link between thimerosal in vaccines and childhood developmental concerns. An excerpt from the study finding reads:

... some people believe increased exposure to thimerosal (from the addition of important new vaccines recommended for children) explains the higher prevalence in recent years. However, evidence from several studies examining trends in vaccine use and changes in autism frequency does not support such an association. Furthermore, a scientific review by the Institute of Medicine (IOM) concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism." (CDC, 2007, p. 144.)

Thompson et al. (2007) further examined the hypotheses that "increasing exposure to thimerosal is associated with neurodevelopmental disorders. Findings did not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years" (Thompson et al., p. 1,290).

Recent Events

As a result of public concern about autism and vaccines, thousands of claims have been submitted to the National Vaccine Injury Compensation Program. On February 12, 2009, the U.S. Court of Federal Claims published decisions about these claims, which were considered as a group under the Omnibus Autism Proceeding. The Court found, after reviewing 5,000 pages of transcripts, 939 medical articles, 50 expert reports, and hearing testimony from 28 experts, that the MMR and thimerosal-containing vaccines, independently or together, were not causal factors in the development of autism or ASD (U.S. Court of Federal Claims, n.d.).

How Do I Apply This Evidence to Nursing Practice?

Studies about vaccination and autism are often complex and difficult for consumers to access and review. Yet it is critical that the findings are shared widely to assure all healthcare professionals have this information in order to provide evidence-based information to parents. Providers can guide parents in their review of available vaccine information. A systematic framework can be utilized by parents to assure the available information is reliable. An excellent tool for reviewing information is available on the American Academy of Pediatrics Web site: <http://www.cispimmunize.org/fam/facts/FAQ-Internet.pdf>. Rigorous scientific studies have not identified concerns with thimerosal in vaccines or the measles, mumps, and rubella vaccine. Vaccines continue to be a vital tool in the prevention of vaccine-preventable disease.

Nurses are often in the unique position of providing advice regarding vaccines in their formal practice areas as well as in their daily lives. Many consider nurses to be experts in all areas of health care, leading neighbors, patients, and others to ask for and value their opinions. Nurses participate in this crucial aspect of the prevention of diseases, and therefore, should have a thorough and complete understanding of the issues, concerns, and facts as related to vaccines. It is imperative that nurses have knowledge of the research and its results, and the information pertaining to the diseases we seek to prevent when discussing vaccines with parents, peers, and medical health professionals.

Nurses should continue to learn about vaccines in order to provide complete and up-to-date information to patients and clients. Excellent vaccine information resources are available online at <http://www.immunize.org>, <http://www.vaccinesafety.edu>, and <http://www.cdc.gov/vaccines>.

Author contact: lisa.miller@state.co.us, joni.reynolds@state.co.us, with a copy to the Editor: roxie.foster@UCDenver.edu

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