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## Childhood Vaccination and Autism

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## INTRODUCTION

Autism is a developmental disorder where children have issues with social interaction ranging from mild to disabling. Autism is diagnosed by certain behaviors including inability to make friends or start a conversation, lack of imaginative play, or repetitive actions (Autism Fact Sheet, 2006). Behavioral problems can be mild to severe and can be impulsive or obsessive behaviors (Twedell, 2008). The World Health Organization's International Classification of Diseases, 10<sup>th</sup> Edition (ICD-10) provides criteria to diagnose autism (Prior, 2003).

Autism has become more prevalent in the last several years. The CDC reported a prevalence of 1 per 500 to as low as 1 per 166 children. These values are taken from recent studies done in many countries. It is found among all races, ethnicities, and socioeconomic groups. Boys are four times more likely than girls to be autistic (Twedell, 2008). Today, this condition is considered more often due to an increase in public and professional awareness. There are more services available to patients with autism so the diagnosis is easier to make if the child will receive needed intervention. Publicity of autism through the media has also increased its awareness by the public (Prior, 2003). Changes in diagnostic criteria and more informed diagnosticians could affect the prevalence of autism today. An increase in autism may easily be explained by under-diagnosis in previous decades (Taylor, 2006).

The cause of autism is not totally understood, but had been linked to genetics and environment (Autism Fact Sheet, 2006). A recent study suggests prenatal exposure to organochlorine pesticides as a possible environmental cause of autism (Twedell, 2008). Autism most likely has a genetic component as monozygous twins are usually concordant for autism and autism within a family is likely. Autism is associated with many medical conditions so there is a biological component (Taylor, 2006). Recent research suggests problem with synapse structure and function causing "brain under-connectivity." Mothers of children with autism may have specific serum antibodies that may be linked to the development of autism. Many interacting genes and environmental interactions lead to an autistic phenotype. There is no single cause for autism (Rapin & Tuchman, 2008).

Autism does not have a cure, but there are therapeutic options and the earlier the treatment, the better the outcome. Treatments include educational or behavioral interaction to help children with social and speech development. Family counseling can be beneficial as well. Medication is used to prevent seizures and anti-depressants may be used if depression or obsessive compulsive disorders are present. There are also many controversial therapies that need further study to prove if truly helpful (Autism Fact Sheet, 2006).

Healthy People 2010 has a goal of 90 percent vaccination in children. By reaching this goal, the risk of outbreaks of many diseases would be decreased. By age two, children should receive up to 24 injections including immunizations for hepatitis A

and B, polio, influenza B, measles, mumps, rubella, pneumonia, meningitis, diphtheria, tetanus, and whooping cough. As many as 2.1 million children in the United States aren't receiving their vaccinations. Some of the non-vaccination is due to increased recommendations with little increase in funding (Thompson, 2007). A likely future cause for decreases in vaccination may be due to public perception of a supposed link between vaccination and autism.

In March, 2008, parents of a girl in Georgia were ruled to be entitled to compensation because their daughter developed autistic symptoms after being vaccinated with childhood vaccines (Doheny, 2008). This ruling truly questions the necessity of vaccination for childhood diseases and puts the question in the mind of every parent as to if they should vaccinate their child or not. The purpose of this study is to review literature on the epidemiologic relationship between childhood vaccinations and the development of autism.

## BACKGROUND INFORMATION

Many studies blame thimerosal as the cause of autism from vaccination. Thimerosal is a preservative to protect vaccines from bacterial or fungal contamination. Thimerosal contains ethyl mercury. Little thimerosal is used today in vaccines in the United States, but it is found in some influenza and hepatitis vaccines (Asif & Roberts, 2006). By age two, a child following the recommended schedule of vaccinations received 100 ug of ethyl mercury in 1990, 237.5 ug in 1999, and less than 40.2 ug in 2004 (Schechter & Grether, 2008). Environmental Protection Agency guidelines for mercury ingestion are applied to vaccination content, but the guidelines are set for methyl mercury and not ethyl mercury. Methyl mercury crosses the blood brain barrier and ethyl mercury does not (Asif & Roberts, 2006). Low dose prenatal exposure to methyl mercury is known to cause neuron-developmental problems and toxic levels of methyl mercury result in symptoms similar to autism (Madsen, et al., 2003). There is some question as to whether comparing the effects of methyl mercury to ethyl mercury is accurate.

Measles, Mumps and Rubella (MMR) is a vaccine that is blamed for causing autism. Andrew Wakefield was the first to link MMR vaccination with autism. His study included twelve children that had autism along with inflammatory bowel syndrome roughly six days after vaccination with MMR (Taylor, 2006). Laboratory evidence in this study found measles virus in bowel biopsy samples. However, this study did not state if the measles was wild type or vaccine strain (DeStefano, et al., 2004). This study was spread rapidly by the media and MMR vaccination declined because of it; epidemics of these three diseases have also occurred since this study. The study lacked controls and case validation. To make matters worse, many of the children were involved in lawsuits against the MMR vaccine company (Taylor, 2006). Wakefield received funding to find a link between vaccination and autism to help their case. Soon after these findings, ten of the original authors of the study retracted their findings in light of Wakefield's research misconduct (Asif & Roberts, 2006).

## REVIEW OF LITERATURE

### Brinkman: Childhood Vaccination and Autism

#### THIMEROSOL AND THE OCCURRENCE OF AUTISM: NEGATIVE ECOLOGIC EVIDENCE FROM DANISH POPULATION-BASED DATA

This population based cohort study was done in Denmark. They were looking at children between two and ten years old and were comparing autism rates before and after the removal of thimerosal from vaccines to see how the rates compare. Vaccination is free in Denmark with coverage around 90 percent. There were 956 children diagnosed with autism between 1971 and 2000. Incidence rates were calculated by taking the number diagnosed with autism in an age group and divided by the total number of children in the age group living in Denmark during that year. Information was taken from the Danish Psychiatric Central Research Register. The incidence of autism was stable before 1990 and incidence increased after 1991. Thimerosal was removed from vaccines in Denmark in 1992. There was no increase during the time thimerosal was used and there was an increase after its use ended, so thimerosal does not cause autism (Madsen, et al., 2003).

Confounding factors in this study include the assumption that the majority of children were vaccinated, but no direct correlation between those diagnosed with autism and their vaccination status. The authors state that at the levels of thimerosal used in Denmark, no association can be made, but if higher levels were used there may be a cause for developmental disorder. The authors suggest that the increase in autism diagnosis could have been caused by increased attention to the syndrome or a change in diagnostic criteria (Madsen, et al., 2003).

#### ASSOCIATION BETWEEN THIMEROSOL-CONTAINING VACCINE AND AUTISM

This cohort study included children born in Denmark from 1990-1996. The sample size was 467,450 children. The hypothesis tested in this study was a comparison of children vaccinated with a thimerosal containing whole cell pertussis vaccine versus one that did not contain thimerosal and subsequent development of autism or autism spectrum disorder (ASD). From 1970 to 1992, a thimerosal preserved whole cell pertussis vaccine was used and from 1992 to 1997, a whole cell pertussis vaccine without thimerosal was used (Hviid, et al., 2003).

Using the Danish Civil Registration System, information on vaccination and autism or ASD diagnosis was compiled. The child's identification number was used to link vaccination information and autism diagnosis information. Doses of vaccine given before June 1992 were considered thimerosal containing and after June 1992 were considered thimerosal free. Diagnosis of autism was defined by the ICD-10. Follow up began at one year of age because autism is rarely diagnosed before one year. There were 2,986,654 person years of follow up with 440 cases of autism and 787 cases of autism spectrum disorder. Follow up of 5770 children was ended due to death, emigration, disappearance or other disease (Hviid, et al., 2003).

Among those receiving at least one dose of thimerosal containing vaccine compared to the thimerosal free group, the relative risk for autism was .85 and for ASD was 1.12, but neither was statistically significant. There was also no evidence of a dose response association of ethyl mercury to autism spectrum disorder (Hviid, et al., 2003).



Confounders that were addressed include child's sex, place of birth, birth weight, five minute apgar score, gestational age, mother's age at child's birth, and mother's country of origin. Some doses after 1992 could have contained thimerosal. This was a prospective study so recall bias was eliminated. Vaccination histories should be complete as practitioners are reimbursed for vaccination so they would be more apt to send in appropriate paperwork (Hviid, et al., 2003).

They found no dose-response relationship with ethyl mercury and autism. No evidence of association between thimerosal in vaccine and autism. The author discussed that ethyl mercury has a shorter half life than methyl mercury and that it is rapidly eliminated (Hviid, et al., 2003). The vaccines were the same formulation with or without the thimerosal so that makes a valid comparison.

#### AN EVALUATION OF THE EFFECTS OF THIMEROSOL ON NEURODEVELOPMENTAL DISORDERS REPORTED FOLLOWING DTP AND HIB VACCINES IN COMPARISON TO DTPH VACCINE IN THE UNITED STATES

This case control study's goal was to evaluate the relationship between thimerosal containing vaccines and autism in the US. This study states that thimerosal is still used in vaccine in the United States. At the time of this study, children received 237.5 ug of mercury by 18 months of age. If given three doses of influenza vaccine the amount was increased to 275ug. As the Center for Disease Control and Prevention (CDC) has increased childhood immunization requirements, the incidence of autism has increased (Geier & Geier, 2006).

Vaccine Adverse Event Reporting System (VAERS) was used to compile data on developmental disorders following vaccination with diphtheria-tetanus-pertussis (DTP) vaccine versus diphtheria-tetanus-pertussis-Haemophilus influenzae type b (DTPH) vaccines. The use of a DTP vaccine adds 100 ug of mercury to the dose as Haemophilus influenzae type b (Hib) vaccine is given with DTP; it is not given additionally if DTPH is administered. The analysis included comparison of the two types of vaccine given in an age-matched population. The number of doses distributed of each vaccine was used to approximate the number of doses given and this number was used to calculate incidence rates. The events evaluated within the VAERS system included autism, mental retardation, speech disorders, thinking abnormalities, infantile spasm and ataxia. Events used as controls to evaluate accuracy in the VAERS system included conjunctivitis, encephalitis, urinary tract infection, and febrile seizures (Geier & Geier, 2006).

The CDC Biological Surveillance Summaries were used to determine the number of doses distributed of each vaccine. DTP was administered to 3,571,475 children and DTPH was given to 33,084,460 children between 1994 and 1998. Both cohorts were similar in distribution, health status, and geographical dispersion. More adverse events of neuron-developmental disorders were reported following DTP vaccination than DTPH vaccination. The increased risk included all disorders but mental retardation (Geier & Geier, 2006).

Potential problems with using VAERS database include underreporting, errors in reporting, multiple exposures, multiple outcomes, or imprecise denominators. Limitations with the system should be similar between the two vaccination groups so is

not a problem according to the author. There is not a “thimerosal free control” group to compare to. Also, other sources of mercury could be significant, but the authors feel that the amount of additional mercury exposure would be similar between the two groups (Geier & Geier, 2006).

This study brings up some good points. There are a lot of variables that are assumed to be similar between the two groups. The lack of a thimerosal free group is unfortunate, but there is probably not any way around that. Finally, they only talk about mercury, but other studies have pointed out the difference between ethyl and methyl mercury; the difference should probably be addressed in this study.

#### CONTINUING INCREASES IN AUTISM REPORTED TO CALIFORNIA’S DEVELOPMENTAL SERVICES SYSTEM

This cohort study looked at prevalence rates of autism as reported to the California Developmental Services System (DDS) in comparison to decreasing levels of thimerosal in childhood vaccines. Data was obtained from the client developmental evaluation reports that are maintained by the DDS. Prevalence was calculated by number of autistic cases reported to the DDS by birth year divided by the number of live births in California for that calendar year. Prevalence was also calculated for the age group of three to five year olds by the number of autistic cases report to the DDS for the age group divided by the number of live births in the cohort, or by the number of three to five year olds living in California for the time period. Thimerosal exposure was assumed in the three to five year olds to be less after 2004 and higher from 1995-2003. The three to five year age group was concentrated on because children are seldom reported to the DDS before three years of age (Schechter & Grether, 2008).

Prevalence in three year olds was calculated to be .3 per 1000 births in 1993 and 1.3 per 1000 births in 2003. The prevalence in three to five year olds has increased since 1999 when thimerosal exposure began to decrease. The authors concluded that autism continued to increase with decreasing exposure to thimerosal (Schechter & Grether, 2008).

Confounding variables in this study include a possibility of substitution of diagnosis in obtaining data from the DDS reports. No actual data was collected on thimerosal exposure, it is assumed by age of child at time of vaccination. Also, other sources of mercury are not considered (Schechter & Grether, 2008).

#### AGE AT FIRST MEASLES-MUMPS-RUBELLA VACCINATION IN CHILDREN WITH AUTISM AND SCHOOL-MATCHED CONTROL SUBJECTS: A POPULATION-BASED STUDY IN METROPOLITAN ATLANTA

This is a case control study with 624 cases and 1824 controls. They compared the age at first MMR vaccination between normal and autistic children. The hypothesis tested by this study was that if MMR vaccination increased autism and that autism develops before 24 months of age, then vaccination at a younger age should cause an increase in the risk of developing autism. They found that the overall distribution of age at first MMR vaccination was similar for case and control children with most between 12-17 months of age (70.5% of cases, 67.5 % of controls). Vaccination before 36 months of age was most common in case children (DeStefano, et al., 2004).

Confounding factors of this study include the fact that date of onset of autism is not always clear. The time of diagnosis may not truly reflect the time the syndrome began. The controls were vaccinated; there was not a non-vaccinated control group. Vaccination records for only two-thirds were analyzed due to children moving or changing schools. Special education for case children may have required additional MMR vaccination compared to control children (DeStefano, et al., 2004).

Strengths of the study include that a panel of experts reviewed the cases to confirm diagnosis of autism. Vaccination history was from standard forms, so there is no recall bias. Behavioral records were used to evaluate demographic and birth characteristics to control for potential confounding variables (DeStefano, et al., 2004). The hypothesis tested by this study only makes sense; it was a more specific hypothesis to be tested than most of the other studies.

#### A POPULATION-BASED STUDY OF MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM

This study was a retrospective cohort study of all children born in Denmark between 1991 and 1998. Of 537,303 children, 440,655 received MMR vaccine. There were 316 diagnosed with autism and 422 diagnosed with other autism spectrum disorders. The hypothesis tested was whether MMR vaccination causes autism or not. Data was obtained from the Danish Civil Registration System and five other national registries (Madsen, et al., 2002).

The MMR vaccinated groups were divided by age at vaccination, interval since vaccination, and calendar period of vaccination. There was follow up of 1,647,504 person years for those vaccinated and 482,360 person years of follow up for those non-vaccinated. Those diagnosed with Autism or ASD were removed from follow up at time of diagnosis (Madsen, et al., 2002).

The study concluded that there is no increased risk of autism or ASD among those vaccinated versus those not vaccinated. There also was no association between autism and age at vaccination, interval between vaccination, and calendar period of vaccination. There are three arguments to support the conclusions: the risk of autism is similar in vaccinated versus non-vaccinated, there was no clustering of cases at a time point after vaccination, and this was a nationwide study with complete follow up (Madsen, et al., 2002).

Confounding variables that were adjusted for include age, sex, calendar period, socioeconomic status, mother's educational level, gestational age, and birth weight. Information was collected prospectively so limited recall bias. Data on vaccination was collected independently of data on autism diagnosis (Madsen, et al., 2002). Adjustments were made for many confounding variables in this study and the author's arguments to support their conclusions are plausible.

#### AN EPIDEMIOLOGICAL STUDY ON JAPANESE AUTISM CONCERNING ROUTINE CHILDHOOD IMMUNIZATION HISTORY

This is a case control study of children with autism in Japan. It tests the hypothesis that MMR vaccination causes autism. The Tokyo Metropolitan Umegoaka Hospital works with 130 school age autism patients. Consent was given and records were

analyzed for this study. The records were analyzed for birth year, ages of initial symptoms, age at diagnosis, and family history of ASD. Vaccination records listed vaccination dates, type, lot number, provider's name, and adverse events. If vaccination occurred after diagnosis, these were considered as non-vaccinated. The control group was chosen from 1700 children born in the same birth year cohort and using one of two pediatric clinics in Tokyo. There were 21 cases enrolled in the study (Takahashi, et al., 2003).

Odds ratios were calculated for increased risk of the case group for the following vaccinations: monovalent measles, monovalent mumps, monovalent rubella, non-mumps, and non-rubella. The entire control group received either MMR or monovalent measles vaccine so and odds ratios for non-measles antigen could not be calculated. Statistically significant increased odds ratios to development of ASD were found with measles, non-mumps, and non-rubella vaccinations. The authors concluded that there was not a harmful causal association with MMR and other vaccinations in Japanese children with ASD (Takahashi, et al., 2003).

The author states that the results of the study may be exaggerated due to the small sample size. Other confounding variable include that parents of cases wanted minimum vaccination, but parents of controls often wanted maximum vaccination. Many infants get measles before they are one in Tokyo, so the vaccination rate is lower for measles in Tokyo; comparison with this rate may be inaccurate. A causal association is dependent on timing of vaccination and onset of disease, however, autism "time of onset" is often hard to determine (Takahashi, et al., 2003).

As the author points out, this would be a better study if the sample size was larger. This study was somewhat confusing because the odds ratios show an increased risk, but the author concludes no causal association. It is assumed that the data is not statistically significant.

## CONCLUSION

In choosing this topic, I was very sure that childhood vaccinations did not cause autism. In reading the studies and other information about autism and why it is thought that vaccination causes autism, my opinion wavered at times. The studies presented in this paper discuss whether autism is caused by the vaccine preservative thimerosal or by the MMR vaccine. Three of the four studies involving thimerosal concluded that it did not cause autism. As thimerosal levels were decreased in the vaccine, there was an increase in cases of autism. The study that supports that thimerosal causes autism compared the dose of mercury given if one vaccination was given or if two vaccinations were given to cover the recommended antigens. Much of the discussion of this study was spent defending why their study was accurate. The three studies concerning MMR vaccination as a cause of autism all concluded that MMR vaccination did not increase the incidence of autism. There are many theories of genetic based causes of autism or genetics together with environment; it will be interesting to see the results of future testing of these theories. Based on what was learned through writing this paper, I have to agree with the current medical community's opinion; vaccination does not cause autism.



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