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Centers for Disease Control and Prevention: Immunization Safety and Autism
Thimerosal and Autism Research Agenda

Study	Description	Study Design	Estimated Publication Date	Study Objective(s)
Autism and Thimerosal-Containing Vaccines: Lack of Consistent Evidence for an Association	This study was prompted by findings reported to the Institute of Medicine by Blaxill in July 2001, which showed increases in autism incidence in California in association with increases in the use of thimerosal-containing vaccines during the 1990s. To further examine the plausibility of this finding, this study took advantage of the cessation of thimerosal use in Denmark and Sweden in 1992 to conduct a before and after comparison of the incidence or case numbers of autism. In both countries, autism increases throughout the years 1987-1999, contrary to the decrease in autism that would be expected after 1992 if thimerosal exposure was related to autism. The increasing trend for autism is most notable in Denmark where the number of autism cases rises substantially even after the discontinuation of thimerosal use. The results were published in the *American Journal of Preventive Medicine* (Aug 2003; 25(2):101-6).	Ecological Cohort	**Published** in *American Journal of Preventive Medicine*, August 2003	Autism
Thimerosal Screening Study	The Vaccine Safety Datalink (VSD) was used to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of renal, neurologic and developmental problems. In the first phase of this study, CDC used data from the two VSD managed care organizations (MCOs) with automated outpatient data (where more subtle effects of mercury toxicity might be seen). The CDC and VSD researchers found statistically significant associations between thimerosal and two neurodevelopmental disorders - language delays and tics. However, the associations were weak and were not consistent between the two MCOs. No association was shown with autism. In the second phase of the investigation, CDC investigators examined data from a third MCO with similar available automated vaccination and outpatient databases to see if these findings could be replicated. Analyses of these data using the same methods as with the first two MCOs did not confirm results seen in the first phase. The results were published in *Pediatrics* (Nov 2003; 112(5): 1039-48). **Presented at the July 2001 IOM Meeting**: **Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes**	Cohort	**Published** in *Pediatrics*, November 2003	Language Delay; Speech Delay; ADHD

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Thimerosal Neurological Developmental Disorders (NDD) Follow-up Study	The Thimerosal Follow-Up Study examines more rigorously the hypotheses that increasing exposure to thimerosal is associated with neurodevelopmental disorders. In contrast to the Thimerosal Screening Study, which utilized ICD-9 codes, the Thimerosal Follow-Up Study will objectively measure the neurodevelopmental disorders of interest by bringing children aged 7 to 9 years into a health clinic for a three-hour objective assessment by staff trained to administer neuropsychological test batteries. The results of the study should be significantly less vulnerable to the introduction of health care seeking bias and will assist in the interpretation of the results obtained in the Thimerosal Screening Study. The study found only a few statistically significant associations between exposure from thimerosal and neuropsychological functioning. The weight of the evidence from this study does not support an association between early ethyl mercury exposure from thimerosal-containing vaccines and/or immunoglobulins and neuropsychological functioning at ages 7 to 10 years. The results published in New England Journal of Medicine (2007 Sep 27;357(13):1281-92). **2001 IOM Recommendation: Thimerosal 4**	Cohort	**Published** in *New England Journal of Medicine*, September 2007	Language Delay; Speech Delay; ADHD
Italy Thimerosal NDD Study	CDC funded this follow-up study in Italy that compares neuropsychological outcomes of children at ages 10-12 years who were randomly assigned to receive one of two forms of diphtheria-tetanus-acellular pertussis vaccine (DTaP) in the first year of life, one containing thimerosal and the other containing 2-phenoxyethanol. As a result, children who received the thimerosal-containing DTaP vaccines had a higher cumulative exposure to thimerosal (137.5 micrograms of ethylmercury) in their first year compared to the other form of DTaP (62.5 micrograms of ethylmercury) during the same age range. Ten years after vaccination, the two groups were tested in school on 24 neuropsychological outcomes. The overall results of the study do not support neurological or developmental harm to children resulting from thimerosal exposure. This strong study adds to the body of scientific evidence that thimerosal in vaccines is not harmful to children. The results are published in Pediatrics (2009 Feb:123(2): 475-482). **2001 IOM Recommendation: Thimerosal 2**	Clinical Trial	**Published:** *Pediatrics*, February 2009	Language Delay; Speech Delay; ADHD

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VSD Thimerosal and Autism Case Control Study	Exposure to thimerosal has been hypothesized to be associated with the risk for autism. Preliminary results from the VSD Thimerosal Screening Study published in 2003 did not find an association between thimerosal exposure and autism risk and recent ecological studies have not found a correlation between thimerosal content of vaccines and autism rates. Autism, however, can be difficult to diagnose and the studies to date have relied on computerized clinical or administrative databases in which the validity of the autism diagnoses have not been fully validated. The Thimerosal and Autism Study is a case-control study conducted in three U.S. MCOs. Data collection began in 2005 and took three years to complete. In this study, children who were diagnosed with autism were matched with control children. The autism diagnosis of the case samples was confirmed by a standardized clinical assessment protocol. Vaccination histories and information on other potential confounding factors were confirmed by reviewing the medical records for all children. In addition, the mothers of both cases and matched controls were interviewed. The IOM Immunization Safety Review Committee recommended such a study in 2001. **2001 IOM Recommendations: Thimerosal 1 & 4**	Case-control	January 2010	Autism
Trends in Diagnosis Rates for Autism and ADHD at Hospital Discharge in the Context of Other Psychiatric Diagnoses	Data from the Healthcare Cost and Utilization Project (HCUP) were used for descriptive analyses of secular trends of diagnosed psychiatric disorders between 1989 and 2000. The HCUP Nationwide Inpatient Sample (NIS) approximates a 20% sample of U.S. community hospitals as defined by the American Hospital Association (AHA). The AHA defines community hospitals as "all nonfederal, short-term, general and other specialty hospitals, excluding hospital units of hospital institutions." Psychiatric disorders were coded using the International Classification of Diseases, 9th edition (ICD-9) (27). Disorders were associated with a hospital discharge if they were coded as the primary or secondary diagnosis for that discharge. For each disorder or set of disorders, three sets of rates were calculated. The rate of hospital discharges associated with each disorder was calculated for each calendar year as a function of the total number of hospital discharges for that year. Average rates were calculated across all years of the study period by year of age. Differences in trends in diagnosis were examined for each period. The results were published in January 2005 in the journal *Psychiatric Services* (January 2005 56:56-62). **2001 IOM Recommendation: Thimerosal 3**	Ecological Cohort	**Published** in *Psychiatric Services*, January 2005	Autism; ADHD

MMR and Autism Research Agenda

Study	Description	Study Design	Estimated Publication Date	Study Objective(s)
Denmark MMR/ Autism Study	CDC has an ongoing cooperative agreement with the Danish Medical Research Council. This cooperative agreement supports a collaborative research program with Danish researchers and provides opportunities for CDC to pursue causes of birth defects and developmental disabilities through Denmark's unique public health data infrastructure. The Danish study, which followed more than 500,000 children, over 7 years, found no association between the MMR vaccination and autism. The results were published in the *New England Journal of Medicine* (2002; 347:1477-82). **2001 IOM Recommendations: MMR/Autism 1, 2, 5, 6**	Cohort	**Published** in *New England Journal of Medicine* November 2002	Autism
Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP)	CDC conducted this study using data collected through the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP). This case-control study examined the possible relationship between exposure to the MMR vaccine and autism. Cases are children with a diagnosis of autism spectrum disorder according to DSM-IV criteria that were between the ages of 3-10 years of age in 1996 and identified through MADDSP. Controls are matched 3:1 with cases based on school system, birth date and gender. Developmental and immunization histories were collected from education records. The study found that the overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children; most case and control children were vaccinated between 12 and 17 months of age. The results were published in *Pediatrics* (Feb 2004; 113(2):259-66). **2001 IOM Recommendations: MMR/Autism 1, 2, 5, 6**	Case-Control	**Published** in *Pediatrics*, February 2004	Autism

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Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study	CDC supported a case-control study to investigate the association between MMR vaccine, gastrointestinal tract disorders (GI), and autistic spectrum disorder (ASD) through examination of intestinal tissue samples for measles virus genome. The research was led by scientists at Columbia University Mailman School of Public Health and included researchers from Massachusetts General Hospital, Trinity College Dublin, and CDC. Laboratories evaluated bowel tissues from 25 children with autism and GI disturbances and 13 children with GI disturbances alone (controls); only 2 biopsy samples with measles virus RNA were found, one in the autism/GI group and one in the control group, showing that the presence of measles virus sequences was not associated with an autism diagnosis (autism/GI group, 4%; control, 8%). Samples were analyzed in three separate laboratories blinded to diagnosis, including one laboratory wherein the original findings suggesting a link between measles virus and autism had been reported in 1998 (Wakefield et al.). Results are inconsistent with a causal role for MMR vaccine as a trigger or exacerbator of either GI difficulties or autism, The results were published in PLoS One (September 2008; 3(9): e3140. doi:10.1371/journal.pone.0003140) **2001 IOM Recommendations: MMR/Autism 2 & 3**	Case-Control	**Published** in PLoS ONE 3(9): e3140. doi:10.1371/journal.pone.0003140	Autism