

Does thimerosal or other mercury exposure increase the risk for autism?

A review of current literature

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This report reviews current literature regarding the association of the pharmaceutical preservative thimerosal and other mercury exposures with the risk for autism. The evidence presented here does not support a causal association between autism and mercury exposure from the preservative thimerosal. The risk for autism from other mercury exposures such as from dental amalgam restorations or environmental mercury release into the atmosphere is ambiguous. Since mercury is a known neurotoxin, more research should be done to ensure that mercury exposure from any source does not contribute to autism.

Key words: autism, mercury, thimerosal, amalgam, risk

INTRODUCTION

Autism, also called autistic disorder, is the most severe of the autism spectrum disorders (ASD's) that also includes Asperger syndrome and pervasive developmental delay - not otherwise specified. In the United States, the Centers for Disease Control and Prevention estimates the current prevalence of ASD's to be one percent of all children (Centers for Disease Control and Prevention 2009). Autism is a developmental disorder defined by social and communication deficits and abnormal repetitive behaviors that are seen in early childhood (American Psychiatric Association 1994). A small percentage of cases of autism are associated with known congenital conditions; however, most cases of autism have an unknown etiology (Fombonne 1999). Autism can affect children in any family and has no ethnic or social boundaries (The Autism Society 2010).

For some children environmental factors may contribute to an increased risk for autism (Becker and

Schultz 2009, Lawler et al. 2004, Schultz 2008, Schultz et al. 2006, 2008). Theories about possible environmental triggers for autism include lack of breastfeeding, use of infant formula without docosahexaenoic acid and arachidonic acid supplementation, childhood vaccinations, acetaminophen and other analgesic use, viral infections, and other environmental exposures. Due to its known neurotoxicity, mercury has been an exposure of interest. Mercury exposures from the pharmaceutical preservative thimerosal and from environmental mercury, particularly in pollution from coal-burning power plants and dental amalgam restorations, have recently been explored as possible risk factors for autism or other ASD's.

MERCURY EXPOSURE FROM THE VACCINE PRESERVATIVE THIMEROSAL

The mercury preservative thimerosal was previously included in childhood vaccines and has been explored as a possible risk factor for autism. Except for the multi-dose influenza vaccine, this preservative has been eliminated or reduced to trace levels in all commonly recommended childhood vaccines in the United States (US Food and Drug Administration 2009) and

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Canada (Fombonne et al. 2006). Autism prevalence, however, continues to increase even after thimerosal was effectively removed from childhood vaccines according to reports from California (Schechter and Grether 2008) and Canada (Fombonne et al. 2006).

Thimerosal is an organomercury compound which contains approximately 49% mercury by weight. Multiple studies by the same researchers (Geier and Geier 2003a, 2003b, 2004, 2006, 2007) and by Dr. Young in association with these researchers (2008) reported an association of thimerosal with neurodevelopmental disorders, including autism. Studies by other researchers including three cohort studies (Andrews et al. 2004, Hviid et al. 2003, Verstraeten et al. 2003), a case-control study (Croen et al. 2008), a cross-sectional study (Miles and Takahashi 2007), and an ecologic study (Madsen et al. 2003) reported no association of thimerosal with autism. A cohort study by Heron and colleagues (2004) investigated developmental disorders and did not find an association with thimerosal exposure, and a cross-sectional study by Thompson and colleagues (2007) found no association between neuropsychological functioning and exposure to thimerosal from mercury-containing vaccines or immune globulins. The association between autism and exposure to thimerosal remains controversial.

The first two studies by Geier and Geier have multiple methodological concerns as reported by Parker and colleagues (2004) that make their data noncontributory to the thimerosal/autism discussion. These studies used the Vaccine Adverse Events Reporting System (VAERS) as their data source which is unsuitable for this purpose (Goodman and Nordin 2006). The VAERS system is a passive reporting system to which anyone can report. Goodman and Nordin have shown that most reports to the VAERS system in recent years regarding thimerosal were influenced by litigation. In other words, most of the recent reports regarding thimerosal were related to pending lawsuits for vaccine injury. This severely biases the dataset, and it should not be used as an assessment of causality. Two other studies by Geier and Geier (2004 and 2006) also used the VAERS dataset which makes their conclusions non-interpretable, and they are non-contributory to this review. The studies contributing to this review are presented in Table I.

A study by Geier and Geier that is included in the review of thimerosal is a case-control study from 2007. This is a study of maternal Rh D status in 53 mothers

of children with ASD and 926 mothers of control children. The investigators state that this is a prospective study, but it would more accurately be described as a retrospective or case-control study. In this study, cases and controls were identified and past medical records of the mothers were retrospectively reviewed. Mothers of children with ASD were found to be Rh negative twice as often as control mothers. Although they reported collecting data on thimerosal anti-D immune globulin injections only for the mothers of cases, the authors conclude that the administration of anti-D immune globulin containing thimerosal preservative is responsible for the increased rate of ASD in mothers who are Rh negative. This study did not control for potential confounding variables.

An ecologic study by Young, Geier, and Geier (2008) showed an association between thimerosal-containing vaccines and autism. Since this was an ecologic analysis, there was no measurement of thimerosal exposure in any of the individuals, and their exposure was estimated. Essentially, this study showed that autism and thimerosal exposure from vaccines both increased during the study period. However, the prevalence of autism has continued to increase after the removal of thimerosal from most childhood vaccines (Fombonne et al. 2006, Schechter and Grether 2008).

None of the three cohort studies investigating autism found an association between autism and thimerosal-containing vaccines. Hviid and colleagues (2003) investigated the association between autism and thimerosal-containing vaccines in a controlled cohort study in Denmark. During 2 986 654 person-years of follow-up, no significant association was seen between autism or other autism spectrum disorders and thimerosal-containing vaccines. Further, they did not see any dose-response relationship between autism and the amount of ethylmercury received from thimerosal-containing vaccines.

In a study by the US Centers for Disease and Prevention, Verstraeten and colleagues (2003) investigated the safety of thimerosal-containing vaccines in a retrospective cohort of children. This was a two phased study consisting of 124 170 infants from two health maintenance organizations (HMO's) and an additional 16 717 children from a third HMO. This study found no significant associations between autism and thimerosal-containing vaccines. However, this study did find significant associations between tics and language delay with thimerosal-containing vaccines, but these results were not consistent at all three HMO's. The

investigators were also unable to completely control for potentially confounding variables, and they recommended additional research to resolve their conflicting findings. This study has been criticized by some who feel the second phase was added in an attempt to negate the significant associations seen and are concerned that the lead author has taken a position with a vaccine manufacturer; however, the lead author has responded to his critics (Verstraeten 2004).

A retrospective cohort study was performed by Andrews and colleagues (2004) investigating the association of developmental disorders with thimerosal exposure in the United Kingdom. A total of 109 863 children were assessed for thimerosal exposure based on the number of DTP (diphtheria-tetanus-pertussis) and DT (diphtheria-tetanus) vaccinations received. In the United Kingdom, these were the only vaccines routinely used in their vaccination program that contained the preservative thimerosal. This study did not

find an association between thimerosal-containing vaccines and autism but did find an association with tics. This study controlled for gender, year of birth, month of birth, but not for other potentially confounding variables.

Similarly, no association was seen between thimerosal and autism in a case-control and a cross-sectional study of mothers given anti-D immune globulin preserved with thimerosal. In the case-control study of maternal Rh D status with 400 cases and 410 controls, no association was seen between autism spectrum disorders and Rh negative status of the mothers (Croen et al 2008). Similarly, no association in this study was seen between autism spectrum disorders and mothers' receipt of anti-D immune globulin containing the preservative thimerosal. This study controlled for the potential confounding variables of sex, birth order, plurality, maternal age, maternal race/ethnicity, and maternal education.

Table I

Studies Investigating Thimerosal Exposure with Autism and Other Developmental Outcomes.

	Type of Study	Outcome Measure	Association with Thimerosal Exposure
Andrews et al., 2004	Cohort	Autism	No
Croen et al., 2008	Case-Control	Autism	No
Geier and Geier, 2007	Case-Control	Autism	Yes
Heron et al., 2004	Cohort	Developmental Disorders	No
Hviid et al., 2003	Cohort	Autism	No
Madsen et al., 2003	Ecologic	Autism	No
Miles and Takahashi, 2007	Cross-Sectional	Autism	No
Thompson et al., 2007	Cohort	Neuropsychological Functioning	No
Verstraeten et al., 2003	Cohort	Autism	No
Young, Geier, and Geier, 2008	Ecologic	Autism	Yes

In the cross-sectional study of 214 families with ASD children, Rh negative status in mothers of children with autism was no more common than in the general population (Miles and Takahashi 2007). This study also found that antepartum exposure to Rh immune globulin and Rh incompatibility was no more common in mothers of children with autism than in mothers the general population.

In a study from Denmark, Madsen and colleagues (2003) found negative evidence of an association of autism with thimerosal in an ecologic analysis. This study found 956 children diagnosed with autism during the study period but did not have measured thimerosal exposures. The authors reported that an increase in incidence in autism followed the discontinuation of thimerosal-containing vaccines in 1992.

A prospective cohort study from the United Kingdom by Heron and colleagues (2004), did not find an association between developmental disorders and the use of thimerosal-containing vaccines. This was a longitudinal study of more than 14 000 children; however, it did not specifically address autism. It did find a positive association of poor prosocial behavior at 47 months with exposure to thimerosal by three months of age. This study adjusted for birth weight, gestation, highest maternal education, gender, parity, housing tenure, maternal smoking, child's ethnicity and breastfeeding.

Thompson and colleagues (2007) enrolled 1 107 children in a study to test the neuropsychological effects of early thimerosal exposure. Their conclusions were that their study did not support a causal association between exposure to mercury from thimerosal in vaccines and immune globulins with deficits in neuropsychological functioning. However, they did report an association between thimerosal exposure and one measure of attention and executive functioning. This study adjusted for age, sex, HMO, maternal IQ, family income, maternal education level, single-parent status, score on the Home Observation for Measurement of the Environment scale, and other not-listed variables. This study did not test for autism or other ASD's in the children.

The Institute of Medicine in the US found no link between vaccines and autism (Institute of Medicine 2004). This report "concludes that the evidence favors rejection of a causal relationship between thimerosal containing vaccines and autism." This report cited serious methodological flaws in the studies by Geier and Geier (2003a, b) which make their findings uninterpretable and non-contributory to the thimerosal/

autism discussion. This report also "concludes that the evidence favors rejection of a causal relationship between MMR (measles-mumps-rubella) vaccine and autism". In our own study, we found that acetaminophen use after the MMR vaccine was associated with autism (Schultz et al. 2008) which could have been responsible for a suspected association of the MMR vaccine and autism.

ENVIRONMENTAL MERCURY EXPOSURE AND AUTISM

Other exposures of interest are the possible association of environmental mercury with autism. For this study, environmental mercury is defined as any mercury exposure other than from thimerosal in vaccine or Rh immune globulin injections. These studies included in this review are presented in Table II.

Dental amalgam contains approximately 50% mercury by weight. In testimony before the Subcommittee on Human Rights and Wellness, US House of Representatives, it was suggested that mercury in mothers' dental amalgam restorations may be a risk factor for autism in their children (Fischer 2004). One study has shown that the number of mothers' dental amalgam restorations are correlated with fetal tissue mercury levels (Drasch et al. 1994), and six studies have shown that mercury in human breast milk is correlated with the number of mothers' dental amalgam restorations (da Costa et al. 2005, Drasch et al. 1998, Drexler and Schaller 1998, Oskarsson et al. 1996, Ursinyova and Masanova 2005, Vimy et al. 1997). A recent review did not find adverse health effects from dental amalgam but did not consider the risk for autism (Roberts and Charlton 2009).

A recent randomized clinical trial explored the use of dental amalgam in children and found no neuropsychological effects, but it did find significantly increased urinary secretion of mercury in children with dental amalgam restorations (Bellinger et al. 2006). This study was too small and the age of cases too old to determine if there was an increased risk for autism.

Holmes and colleagues (2003) found a significantly higher number of dental amalgam restorations in the mothers of autistic children compared to the mothers of control children. The methods section described counting of the mother's dental amalgam surfaces by the mother herself with a mirror or by the husband, but the results were reported only for the number of amal-

gam fillings. This study did not adjust for the age of the mothers.

Recently the study “A prospective study of prenatal mercury exposure from maternal dental amalgams and autism severity” was published by Geier and colleagues in the journal *Acta Neurobiologiae Experimentalis* (2009). This study found an association between more severe autism and the number of mothers’ dental amalgam restorations. Geier and colleagues did not adjust for the age of the mother when her child was born. The information on the number of dental amalgam restorations was provided by survey.

An ecological study of Texas found an association between environmental mercury release into the atmosphere and autism (Palmer et al. 2006). Since this was an ecological study, there were no measurements of individual mercury exposures in any of the subjects. This type of study is for hypothesis generation only and needs to be repeated with measurements of actual

mercury exposures in children with and without autism.

Hair analysis for mercury has been used as an estimate of mercury exposure. In a case-control study, maternal hair mercury levels were used as a marker for fetal exposure and was found to be associated with subsequent decreases in children’s cognitive performance (Grandjean et al. 1998). In a study by Fido and Al-Saad (2005), hair samples of children with autism compared to matched controls had significantly more mercury as well as lead and uranium. A case-control study analyzed hair samples from children’s first haircuts as a correlation of environmental exposure to mercury (Holmes et al. 2003). This study found significantly less mercury in the hair of children with autism compared to controls. The authors of this study suggested that children with autism had problems with mercury excretion which could have led to toxic effects from mercury buildup. Also in this study, fully 60% of the mercury in

Table II

Studies Investigating Environmental Mercury with Autism and Other Developmental Outcomes.				
	Type of Study	Outcome Measure	Source of Mercury Investigated	Significant Association Seen with Outcome
Bellinger et al., 2006	Randomized Clinical Trial	Neuropsychological Effects	Dental Amalgam in Children	None
Fido and Al-Saad, 2005	Matched Case-Control	Autism	Hair Mercury in Children	Positive
Geier et al., 2009	Case-Control	Autism Severity	Dental Amalgam in Mothers	Positive
Grandjean et al., 2008	Case-Control	Cognitive Performance in Children	Hair Mercury in Mothers	Positive
Palmer et al., 2006	Ecologic	Autism	Mercury Released into the Atmosphere	Positive
Hertz-Picciotto et al., 2010	Case-Control	Autism	Blood Levels of Mercury	None
Holmes et al., 2003	Case-Control	Autism	Dental Amalgam in Mothers/Hair Mercury in Children	Positive/Negative

the hair of the control children was correlated with the number of mothers' dental amalgam restorations.

A more recent investigation did not find a correlation between blood levels of mercury and status as autism cases or controls (Hertz-Picciotto et al. 2010). In other words, children with autism did not have higher levels of mercury in their blood compared to control children. However, this study did find increased blood mercury levels for children with dental amalgam restorations who chewed gum or ground their teeth. This indicates that agitation of the dental amalgam restorations may increase mercury release.

DISCUSSION

The studies supporting the association of thimerosal with autism primarily come from the same group of researchers and are negated by multiple studies from other researchers (Table I). However, two studies reported an association of thimerosal exposure with tics (Andrews et al. 2004, Verstraeten et al. 2003) which should be further investigated. It is disconcerting that two of the studies reported significant negative associations between thimerosal-containing vaccines with autism and other neurodevelopmental disorders (Andrews et al. 2004, Heron et al. 2004). In other words, it appears as if thimerosal exposure is protective for some of the outcomes investigated. A possible reason could be that after a bad outcome following the administration of a vaccine containing thimerosal, parents refused further thimerosal-containing vaccinations for their children. It is also possible that publicity regarding an association of thimerosal in vaccines with autism could have influenced parents of children with autism to discontinue further vaccinations. If either of these is the case, it could explain the significant negative associations as parents of children with autism or other neurodevelopmental problems did not complete the vaccination schedule. This could make it appear that those who received more thimerosal-containing vaccines were less likely to have a neurodevelopmental problem. Research on this question should be undertaken to determine if this is the case and to ensure that children with autism are getting their required vaccinations.

Seven studies investigating other mercury exposure with autism are presented in Table II. Two studies on relationship of dental amalgam restorations in mothers found a significant association with autism (Holmes et al. 2003, Geier et al. 2009); however, these studies were

not adjusted for the age of the mothers. Since mother's age has been shown to be a risk factor for autism (Durkin et al. 2008) and our own research has shown that the number of amalgam restorations increases with a mother's age, this adjustment is critical. Without this adjustment, the number of dental amalgam restorations could act as a surrogate for the age of the mothers.

The investigation of dental amalgam with autism by Geier and colleagues (2009) claims to be a prospective study; however, the study would more accurately be described as a case-control or retrospective study. This is not a prospective study since the information regarding which participants have more severe autism is known at the beginning of the study. If this were a prospective study, individuals without autism would be enrolled and followed over time for development of autism.

In the studies by Holmes and colleagues (2003) and Geier and colleagues (2009), the lack of a dentist confirmation of both the number of dental amalgam restorations and the number of tooth surfaces covered could have led to errors. Some filling materials, i.e. stainless steel crowns, chrome alloys, platinum gold alloys, non-precious crowns, and semi-precious crowns, are the same color as dental amalgam and could have led to counting errors. Mothers may have been inaccurate about the placement time of their restorations. The dental amalgam restorations of interest are ones in place prior to gestation, during gestation, and for one year following gestation (for mothers who breastfed their child).

Our own research using data provided by the Autism Internet Research Survey did not show an association of autism and mothers' dental amalgam restorations, but our data was also self-reported by the mothers. A more accurate investigation including review of dental records should be undertaken to more fully explore the possible risk for autism from dental amalgam restorations. A randomized clinical trial in older children did not see an increase in neuropsychological problems associated with the use of dental amalgam in children (Bellinger et al. 2006).

The ecological study showing increases in autism near sources of atmospheric mercury pollution (Palmer et al. 2006) was interesting but by itself does not indicate causality. Ecological studies are mainly useful for hypothesis generation. Studies on hair samples in children have shown increased and decreased mercury in the hair of children with autism compared to controls. The study on hair samples in mothers showed an interesting association with cognitive performance in chil-

dren but did not assess autism (Grandjean et al. 2008). The study measuring blood levels of mercury found no difference between cases and controls and lends support to the idea that mercury exposure is not related to autism. More research needs to be done in this area to determine if hair and blood are appropriate vehicles to measure environmental mercury exposure and to investigate possible associations with autism.

CONCLUSIONS

The evidence presented here does not support the association between autism and mercury exposure from the pharmaceutical preservative thimerosal. The evidence is equivocal for an association between other environmental exposures with autism. This report does not attempt to review all of the literature regarding mercury exposure and autism. It does, however, review much of the current controversy surrounding the relationship of mercury and autism. Since mercury is a known neurotoxin, more research should be undertaken to define the relationship between mercury exposure and the risk for autism.

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