

Effects of Vaccine Preservatives and Adjuvants on Childhood Neurodevelopment

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Abstract

Parental concerns about the safety of childhood vaccinations began in the 1990's and continue until today. A primary concern of many parents is whether the adjuvants and preservatives added to the vaccines have the potential to cause neurodevelopmental disorders in young children. An overview of various studies was done to determine if thimerosal affects childhood neurodevelopment with studies suggesting that thimerosal potentially causes neurodevelopmental disorders. However, some studies suggest the opposite. As a result it is impossible to conclude whether thimerosal affects childhood neurodevelopment. However, measures should be taken to remove thimerosal from the childhood vaccination schedule. Additionally, the studies must be done to determine if other components of vaccines can have adverse effects on the developing nervous system.

Introduction

Thimerosal, a mercury-based vaccine preservative, has been a source of controversy since the 1990's. Many parents worried that the presence of mercury in vaccinations could lead to autism spectrum disorder and other medical problems. The Center for Disease Control and the American Academy of Pediatrics collectively decided, in July 1999, to remove thimerosal containing vaccines (Baker, 2007). According to the Food and Drug Administration thimerosal has undergone various studies and it "has a long record of safe and effective use preventing bacterial and fungal contamination of vaccines, with no ill effects established other than minor local reactions at the site of injection" (FDA, 2015). In the United States, the only vaccines that currently contain thimerosal are MPSV4-Menomune (vaccine for meningitis), Td (booster for tetanus and diphtheria) manufactured by Decavac, Td (Mass Biologics), Dt (Sanofi) and three of the influenza vaccines (Hamborsky et al., 2015). Some researchers posit that there may be a link between thimerosal and neurodevelopmental problems. Other studies demonstrate that thimerosal does not have such effects. This study was done to determine if thimerosal poses a risk on childhood neurodevelopment.

Purpose of Preservatives and Adjuvants in Vaccines:

The United States Code of Federal Regulations (CFR) mandates the addition of preservatives to vaccines in vials containing multiple doses to prevent contamination of the vaccine after multiple needle insertions. Previously, some vaccines became contaminated during the manufacturing process. As a result, the CFR required the addition of preservatives to kill the microbes that contaminated the vaccine. With the advancement of aseptic manufacturing of vaccines, the necessity of putting preservatives in vaccines has decreased. As a result, many vaccines do not currently require the addition of preservatives into them (Geier et al., 2010). Adjuvants are added to vaccines to help the body develop immunity after injection of killed vaccines. Adjuvants are added to minimize the amount of antigens the body needs to be exposed to in order to generate an immune response (Petrovsky, Aguilar, 2004).

Methyl Mercury vs. Ethyl Mercury

The main question behind the debate over thimerosal is the

comparison between ethyl and methyl mercury. Mercury exposure has been found to cause severe health problems such as damage to the nervous, digestive and immune systems. Methyl mercury specifically has been found to affect the developing brain and nervous system. The most susceptible individuals to methyl mercury are fetuses exposed to methyl mercury in utero (WHO, 2013). Methyl mercury has been proven to cause neurotoxicity since the 1960's. Mothers who ate fish in water contaminated by methyl mercury during their pregnancy, gave birth to children with mental retardation, blindness, and spasticity. However, mothers exposed to methyl mercury were less adversely affected than the infants. A study on New Zealand neonates born from mothers who had hair concentrations of mercury greater than six micrograms per gram found that infants with greater mercury exposure had a lower Intelligence Quotient (IQ) by three points. The United States National Academy of Sciences decided that fetal exposure to methyl mercury can be toxic even at low concentrations (Grandjean, Landrigan, 2006).

The Food and Drug Administration states that the legal guidelines for mercury exposure were decided based on studies on methyl mercury. However, thimerosal's derivative is ethyl mercury which as a result of being slightly chemically different can have different effects on the body than methyl mercury. Additionally, high levels of ethyl mercury were found to have severe neurological effects on both adults and children. However, the effects of low dose ethyl mercury exposure have not been determined (Offit, Jew, 2003). As there is no definitive study with a safe exposure concentration of ethyl mercury and the differences in the effects of methyl and ethyl mercury are not known, the FDA considers ethyl mercury to be as toxic as methyl mercury (FDA, 2015). Ethyl mercury was found to increase the tissue concentration of inorganic mercury more than methyl mercury does in rhesus macaques (Hornig et al., 2004). Ethyl mercury levels in the brain post exposure are lower than those of methyl mercury (Clements, 2004). A main source of the controversy on thimerosal is the question if methyl and ethyl mercury have the same or different effects on the body. Some studies show that thimerosal's ethyl mercury does indeed have neurotoxic effects, while others argue that it does not.

Methods

A variety of research papers on the subject were collected from Google Scholar, EBSCO and ProQuest. Access to EBSCO and ProQuest was given through the Touro College Library System. Key words used, were thimerosal, neurodevelopment, adjuvants, vaccines, adverse effects and immunizations.

Results

Thimerosal and Neurodevelopment:

Thimerosal Causes Neurodevelopmental Disorders

In the 1990's many infants had mercury exposure higher than that recommended by the EPA, FDA, and the United States Agency for Toxic Substances and Disease Registry (ATSDR) for methyl mercury. This was a result of both Thimerosal Containing Vaccine (TCV) and environmental exposure. Methyl mercury is a compound that is closely related to ethyl mercury, one of the derivatives of thimerosal. A study of 278,624 infants born between 1990 and 1996 and recorded in the Vaccine Safety Datalink was done in order to determine if thimerosal indeed has neurotoxic effects on infants and young children. During those years the main vaccines containing thimerosal were the Haemophilus Influenza Type b (Hib), hepatitis B, acellular DTaP (Diphtheria, Tetanus, acellular Pertussis), and whole-cell DTP. The amount of mercury exposure was calculated for each individual based on the amount and concentration of mercury in each of the mercury containing vaccines. The mercury exposure was measured between two intervals, birth and 7 months and birth and 13 months. The rate of increase in six neurodevelopmental disorders were calculated for each additional 100 microgram of mercury the children were exposed to. Three control disorders were also observed for each 100 microgram increase in mercury exposure due to thimerosal containing vaccines. (Young et al., 2008)

The six neurodevelopmental disorders observed were Autism, Autism Spectrum Disorders (ASD), Hyperkinetic syndrome of childhood (ADD/ADHD), Developmental/Learning Disorders, Disturbances of emotions specific to childhood and adolescence, and tics. The control disorders observed were pneumonia, congenital anomalies, and failure to thrive. The study determined that the ratios of each of these disorders increased with the increased exposure to Thimerosal containing vaccines. The rate ratios were measured with a confidence interval of 95%. For each 100 microgram increase in mercury exposure the ratio of hyperkinetic syndrome of childhood increased by a ratio of 3.15 and Autism and Autism Spectrum disorders increased by ratios of 2.87 and 2.44 respectively. Developmental and Learning disorders had the lowest ratio of increase, while hyperkinetic syndrome had the highest. The control disorders did not have a relatively high increase as a result of higher mercury exposure (Young et al., 2008).

The levels of autism corresponding to each year in the study directly correlated to the amount of mercury exposure via vaccine. In 1990 and 1991, hepatitis B and Hib had been added to the vaccine schedule. After 1992, the DTP vaccine was combined with Hib vaccine, thus leading to a lower mercury exposure than there had been when the two vaccines were kept separate. The levels of autism in those years fluctuate directly with the fluctuations of mercury administered via vaccine (Young et al., 2008).

Another study compared the toxicities of the four most common preservatives added to vaccines in the United States. These four compounds were 2-phenoxyphenol, phenol, Thimerosal, and benzethonium chloride. These compounds were administered to human neurons in vitro and to bacterial cells. The toxicities to each type of cell were measured. The cytotoxicity towards human neuroblastoma cells was measured after 24 hours of incubation. Thimerosal was found to be the most toxic of the four preservatives added to vaccines. Each of the four compounds was also tested on bacterial cells. A thimerosal concentration of ten times the amount added to vaccines was not able to sufficiently kill bacterial cells within twenty minutes (Geier et al., 2010).

While there is room to question the certainty of the thimerosal's effects on children, it is highly likely that thimerosal does adversely affect the neurodevelopment of susceptible infants. In some of the studies thimerosal was the only measured variable, while in others thimerosal was taken into account with other possible neurotoxic environmental exposures. Using the Gesell Development Score, investigators found no correlation between thimerosal exposure from vaccines and neurodevelopmental disorders, if the child nursed for the first six months of life. The GDS was also measured from birth to five years and once again there was no correlation between thimerosal exposure and neurodevelopmental disorders. The studies that took environmental exposure to neurotoxic elements into consideration as well as thimerosal, found that ethyl mercury, one of the byproducts of thimerosal, has adverse effects on neurodevelopment. The controlled variables were the environmental factors that were known to affect neuroplasticity. For example, secondhand smoke, cord blood Hg, and lead (Dorea, 2015).

The Vaccine Adverse Events Reporting System (VAERS) database was used to determine if indeed the rise in childhood neurodevelopmental disorders was caused by thimerosal exposure due to vaccinations. A comparison was made of the prevalence of neurodevelopmental disorders after exposure to either thimerosal containing or thimerosal free DTaP vaccines. Three neurodevelopmental disorders were observed in this study; autism, personality disorders and mental retardation.

The participating patients were split into two groups, the first group had an average mercury exposure of 37.5 microgram, while the second group had a mercury exposure of 87.5 micrograms. Some of the control adverse events were fever, pain, and vomiting. The United States Department of Education report from 2001 was also evaluated to find out how many children in different age groups suffered from a variety of conditions; autism, speech disorders, orthopedic or visual impairments, and deaf-blindness. The amount of mercury the children were exposed to was also compared to the maximum possible amount of mercury exposure allowed by the FDA (Geier, Geier, 2003).

Comparing the prevalence of autism, personality disorders and mental retardation following exposure to thimerosal from the DTaP vaccine and the thimerosal-free DTaP demonstrated a linear correlation between mercury exposure and neurodevelopmental disorders. The odds ratio of autism increased by .029, personality disorders by .012, and mental retardation by .048 for each microgram of mercury. The odds ratio for each of these disorders was higher for each of them after exposure to the DTaP containing thimerosal than for that without it. The United States Department of Education report also had increasing ratios in autism and speech disorders. The amount of febrile seizure, fever, pain, edema, and vomiting was higher for the thimerosal containing DTaP vaccine group, however the amount it rose and the increasing amount of mercury exposure do not directly relate to one another. The study also demonstrated that the amount of mercury the children were exposed to due to the childhood vaccine schedule in different years had 3.2-32 fold higher amount than that recommended by the FDA for oral methylmercury. Exposure to mercury intravenously has more adverse effects on the body than if it has been orally ingested (Geier, Geier, 2003).

A study surveying British children found there to be a relationship between hyperactivity and behavioral problems, motor development and the necessity for speech therapy. Other studies have found that there were significant differences in the impact of thimerosal on different genders. Male children were found to have a higher IQ upon exposure, but the exposure also hampered their behavioral regulation and motor tics. In a study in Italian children thimerosal was found to detrimentally affect girls in the areas of language and motor function (Curtis et al., 2015)

An overview was done by analyzing the results of in vivo and in vitro studies of the thimerosal's effects. In the in vitro studies thimerosal was found to cause mitochondrial damage, reduce oxidation-reduction activity, cause cell degeneration and cell death, and increase the levels of fragmented DNA in human neuroblastoma cells. In some of the overviewed studies the

concentration of thimerosal tested was lower than that found in TCv, while in some the concentration ranged from nano to micromolar concentrations. An In vivo study administered different concentrations of thimerosal to suckling Wistar and Lewis rats at 7, 9, 11 and 15 days. The thimerosal was found to decrease pain sensitivity and to significantly accumulate in rat brains. The concentration of thimerosal found in vaccines had neurotoxic effects on human neurons in vitro and in laboratory animals (Dorea, 2011).

Thimerosal Does Not Cause Neurodevelopmental Disorders

A study was done in Poland to determine if there is a correlation between exposure to Thimerosal containing vaccines and cognitive development in the children's' first nine years. All of these children had been given the DTP and hepatitis B vaccine, some of which contained thimerosal and some which didn't. At different points during the first nine years of life, tests were done to assess the level of each child's cognitive development. All the vaccines that the children were exposed to contained aluminum as an adjuvant. In the first month of life 69.2% of the children were exposed to thimerosal, and between the first month and the 6th month 86.2% of the children were exposed to thimerosal containing vaccines. The results of each psychological test done were similar for both children who were and were not exposed to thimerosal. In fact the IQ levels of those exposed to thimerosal was higher overall than that of the control group. The results of the study displayed no correlation between thimerosal exposure and lower cognitive developmental levels. (Mrozek-Budzyn et al., 2014).

Various studies had been done testing thimerosal containing vaccines on rodents, with results demonstrating that thimerosal had no neurodevelopmental effects. However, on the rare occasion that there was a problem with the vaccine, a very high dosage of thimerosal had been administered, 250 fold higher than contained in vaccines. A study was done to compare the effects of different vaccine schedules on a non-human primate model. These were chosen as their anatomy and length of development stages are very similar to those of humans. Neurobehavioral tests were done on the primates to see the effect of a variety of vaccine schedules on the primates' neurodevelopment (Curtis et al., 2015).

In the study seventy-nine rhesus macaques were split into six groups. The first group, the control, received saline injections. The second group received only the MMR vaccine, the third TCv's excluding the MMR vaccine. The fourth group was administered the vaccine schedule from the 1990's, while the fifth group received the same vaccines with accelerated timing at a ratio of 4:1. The sixth group was administered the vaccine

schedule from 2008. In the 1999 vaccine schedule, the TCV's were Hepatitis B, DTaP, and Hib. In the 2008 vaccine schedule, the multiple-dose influenza and meningitis vaccines contained thimerosal. The pregnant macaques in the 2008 group were given the influenza vaccines a month before the expected delivery date. (Curtis et al., 2015).

Each of the infant macaques was tested on the Neonatal Behavioral Assessment Scale to check for nineteen neonatal reflexes. There was no significant difference in the results of each of the six groups for the NBAS test, except in one of the criteria. The macaques were also tested for their object concept performance, their social behavior and the discrimination/reversal learning and learning set. In each of these tests there were no significant differences in the results among the groups. The animals given TCVs reached their goal in fewer trials than animals in the control group in the reversal learning part of the test. Thereby demonstrating that thimerosal did not hamper this area of neurodevelopment. At the age of 12 months the fifth group had a significantly lower amount of exploring behaviors than did the control macaques. The fifth group also had a lower amount of positive behaviors at 2 months, while at 12 months they had a higher amount of positive behaviors than did the rest at two months of age the fourth and sixth groups had significantly fewer negative behaviors, however at 12 months there were no major differences between the six groups (Curtis et al., 2015).

A study in Denmark, used data from the Danish Psychiatric Central Research Register to determine if thimerosal exposure leads to autism spectrum disorder. This study was done to determine if removing thimerosal from vaccines decreased the incidence of autism. The rates of autism diagnosed from 1971 to 2000 for children in three age groups, ages 2-4, 5-6, and 7-9, were reviewed. From the years 1961 to 1970 the children were administered 400 micrograms of thimerosal. From 1971-1992 children were exposed to 250 micrograms of thimerosal. After 1992, vaccines without thimerosal were administered to Danish children. During this period, 956 children had been diagnosed with autism. From 1971 to about 1990 the rates of autism remained stable. After 1991, the rates of autism began to increase, peaking in the year 1999 with the highest incidences occurring in the first two age groups, between 2 – 6 years of age. Each of these children had been born after thimerosal containing vaccines had been removed from the Danish vaccine schedule. Thereby indicating, that the increase of autism does not relate to thimerosal exposure (Madsen et. al, 2003).

Aluminum and Neurodevelopment

Studies have demonstrated that in vitro aluminum exposure has the potential to cause cell death in human neurons. However,

aluminum has been found to be less cytotoxic than thimerosal (Dorea, Marques, 2009). A study was done to determine if aluminum exposure as a result of its use as a vaccine adjuvant is a cause of the rise of autism. Data was taken from the US Department of Educational Annual Reports to Congress to determine the rates of autism from 1991-2008 for individuals age 6 – 21. The rates of autism were also compared to the aluminum exposure in regards to the vaccine schedule in other countries. The data was compared to the concentration of aluminum exposure from pediatric vaccines, below 6 years of age. Results demonstrated that the highest level of aluminum in comparison was at age 2 months in the United States. Interestingly, the countries with higher aluminum adjuvant exposure had higher rate of autism (Tomljenovic, Shaw, 2011).

Discussion

Based on the reported studies there is room to question the effects of the Thimerosal and vaccines containing it on human children. Studies done in vitro demonstrate that thimerosal does cause apoptosis and neurotoxic effects to human neurons (Dorea, 2011). However, results occurring in vitro are not always a directly comparable to those in vivo, as in vivo it is difficult to accurately evaluate the concentration of mercury reaching the individual's neurons. Additionally, studies done on Rhesus macaques seem to point out that thimerosal does not hinder neurodevelopment, in some cases the exposed animals had scored higher than the control (Curtis et al., 2015). However, the primate model is not necessarily an exact indication as to what would happen to humans when they would be exposed to the same concentrations of thimerosal, though the results would be similar as the two bodies function similarly. Only seventy-nine macaques were surveyed and then split into six groups, thereby only a small number of macaques represented each vaccine schedule. Therefore, even though the macaque functions similarly to humans, the validity of the results in comparison to human would need a higher number of macaques in each group to demonstrate the efficacy of the results.

The study using the Vaccine Safety Datalink uses a large sample of children, and demonstrates a direct correlation between thimerosal exposure and neurodevelopmental disorders. However, the study does not take into account environmental exposure to mercury and other neurotoxins, thereby making it harder to say with certainty that thimerosal does indeed cause different neurodevelopmental disorders (Young et al., 2008). The study also does not take into account the genetics of the children and the possible predisposition to neurodevelopmental disorders. However, there does seem to be a strong indication that thimerosal has neurodevelopmental effects, as the prevalence of autism in various years was directly related to the fluctuations of mercury in the childhood vaccine schedule, thus indicating

that children born in years that a vaccine schedule with a higher concentration of mercury had increased rates of autism.

Additionally, the primate model is not a direct representation of what would happen in the human models because studies show that the rate of elimination in the blood and brain differ for methyl and ethyl mercury in primates and human infants (Hornig et al., 2004). As a result, ethyl mercury in humans may cause different mercury levels than it would for the rhesus macaques used in two of the above studies.

Based on the above studies it is hard to conclude whether or not thimerosal containing vaccines cause neurodevelopmental disorders. However, some studies do seem to indicate that thimerosal causes autism among other neurodevelopmental disorders. Additionally, thimerosal containing vaccines were found to cause a significant amount of damage to human neurons *in vitro*, including cell death. As a result, further study must be done to determine with certainty the true effects of thimerosal on human neurodevelopment.

As one study demonstrated that the concentration of thimerosal found in human vaccines was not sufficient to kill bacterial cells, the question arises as to the necessity of placing thimerosal into vaccines. Additionally, after administration of multiple doses DTP and Td vaccines that contained thimerosal as a preservative there were outbreaks of pyogenic infections. Indicating that despite the addition of preservatives to vaccines, microbial contamination can still occur (Ball et al., 2001). One of the main vaccines today currently containing thimerosal is the multiple-dose influenza vaccine. Thimerosal is added as a preservative to prevent bacterial contamination of the vaccine. If the concentration of thimerosal needed to effectively rid the vaccine of bacteria is higher than the concentration of thimerosal in the vaccine, then it is likely that the thimerosal is not doing its job. Steps should be taken to remove thimerosal from vaccines as there is a strong potential that thimerosal does indeed cause neurodevelopmental problems. If thimerosal is kept in vaccines, it should be determined whether the benefits thimerosal brings to the vaccine outweigh the risks brought onto children when they are vaccinated.

Fetuses, neonates, and other small children are the most susceptible to neurodevelopmental damage, as these are the periods of brain growth (WHO, 2013 and Dorea, 2015). The World Health Organization states a fetus is the most susceptible to neurotoxic factors (WHO, 2016). Additionally, during the prenatal and early postnatal stages the Blood Brain Barrier (BBB) is not fully developed. As a result, the likelihood of neurotoxins crossing the BBB is higher in fetuses and newborns (Tomljenovic and Shaw, 2011). As the risks of thimerosal exist and there is

not conclusive proof that there is not neurotoxicity, injecting pregnant woman and babies with vaccines containing thimerosal should be avoided, as these are the ages most critical to childhood neurodevelopment. For example, the Center for Disease Control currently recommends that the influenza vaccine be administered to pregnant woman as a woman suffering from influenza during her pregnancy is at great risk (Center for Disease Control, 2015). Pregnant women are more likely to have longer stays at the hospital as a result of respiratory illnesses, than when not pregnant (American College of Obstetricians and Gynecologists). There seems to be a clear benefit of a pregnant woman being immunized to influenza. However, based on the information above, there is clearly a potential that thimerosal causes neurodevelopmental disorders, and this stage is where the fetus is the most susceptible to neurotoxins. As a result, measures should be taken to ensure that pregnant women are given the influenza vaccine that does not contain thimerosal. Additionally, the postnatal stages till adolescence are still stages of neurodevelopment. As thimerosal potentially causes neurodevelopmental disorders, the benefits of thimerosal containing vaccines must be evaluated to see if they actually outweigh the risks presented by thimerosal exposure.

Conclusions

There is no definitive evidence to conclusively determine if thimerosal causes neurodevelopmental disorders in young children. However, the potential for thimerosal to cause neurodevelopmental disorders gives rise to question the potential harm of the other agents used as preservatives and adjuvants in vaccine today. One of the main adjuvants used in vaccines today is Aluminum, which does seem to have the potential to affect neurodevelopment, specifically causing autism spectrum disorder. As vaccines are being administered to susceptible individuals, further studies should be done to all the chemicals added to vaccines to determine if they are really safe, and if the benefits they bring to the vaccine outweigh the risks.

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