

DO VACCINES CAUSE AUTISM?

**An Evidenced-Based Review of the Rise in Autism and
Suggested Link to Infant Immunizations**

Centennial Pediatrics

Chad D. Guetersloh, M.D.
Christopher 'Kit' Newton, M.D., Ph.D.
Richard C. Nail, M.D.
Susan M. Weiser, M.D.

INTRODUCTION

Immunizations are arguably the single most successful and cost-effective measure for preventing disease and death in the history of mankind. They not only protect individuals from serious illness, but also prevent spread of infectious disease throughout the entire community. Individuals indirectly protected are often children who are too young or too sick to be immunized and who are susceptible to vaccine-preventable disease. To appreciate the beneficial effect that immunization has had in this country, consider that more than 16% of children born at the turn of the 20th century died before reaching 5 years of age of an infectious disease that is now preventable.

The diseases we currently vaccinate against are all still circulating – some, like pertussis (whooping cough) and influenza, remain common throughout our environment. Others, like measles, are rampant elsewhere in the world and are only a plane ride away.

Despite the incredible track record of vaccines in reducing the burden of childhood disease, suspicion about vaccine safety circulates in some groups. Vaccines have become the victim of their own success, as parents no longer see the reality of the infections that are being prevented. Parents are being exposed to an ever increasing number of claims questioning the safety and legitimacy of infant vaccinations. These fears are often propagated via the media and the internet with arguments that sound compelling even when they are not scientifically valid. Understandably, parents are confused about who or what to believe. Some concerned parents, possibly yourself, are delaying or outright refusing to have their children immunized. This review intends to provide you with an evidence-based overview of the sources of these concerns and the science that addresses them so that you can make a truly informed decision about vaccinating your child. We will not be taking an exhaustive look at all of the claims that have been made about vaccine-related illness but will focus instead on the specific issue of autism since that has received the greatest amount of scrutiny and study. Hopefully a thorough understanding of the vaccine-autism debate will provide a framework to judge other vaccine-disease relationship claims.

AUTISM OVERVIEW

Before addressing the vaccine issue, it is necessary to take a brief look at autism in general. Autism, first formally described independently by Leo Kanner in the U.S. in 1943 and Hans Asperger in Austria in 1944, is a disorder characterized by impairment in social interactions and communication along with restricted interests and stereotyped behavioral patterns. Autism is without a verifiable biological marker (there is no blood test or brain scan to reliably diagnose it), so diagnosis relies instead on descriptive criteria and subjective evaluation. Autism is now viewed as a large spectrum of disorders with varying characteristics and multiple underlying causes. According to the Diagnostic Statistical Manual of Mental Disease, version IV, revised (DSM IV-R) – the manual used by mental health providers to define the criteria for psychiatric disease – the major Autism Spectrum Disorders (ASDs), also referred to by some as Pervasive Developmental Disorders (PDDs), are classified as 1) Classic autism, 2) Asperger's Disorder and 3) Pervasive Developmental Disorder Not Otherwise Specified. Rarer forms of autism include Rett's Syndrome and Childhood Disintegrative Disorder. The diagnostic criteria for each of the major autism classes are reviewed in the table below.

Characteristics of Pervasive Developmental Disorders	
Disorder	Characteristics
Autistic disorder (classic autism)	<ul style="list-style-type: none"> • Presence of ≥ 6 of 12 potential deficits involving all three behavioral domains that define the autistic spectrum: <ul style="list-style-type: none"> ≥ 2 deficits in sociability, empathy, and insight into other persons' feelings and agendas ≥ 1 deficit in communicative language and imagination ≥ 1 deficit in behavioral and cognitive flexibility • Detectable before the age of 3 years • Diagnosis not excluded by the level of cognitive competence or the existence of other handicaps
Asperger's disorder	<ul style="list-style-type: none"> • Troublesome social ineptness, lack of insight • Behavioral inflexibility with a narrow range of interests • IQ ≥ 70 (affected children may be normally intelligent or gifted) • No delay in the emergence of speech • Often clumsiness
Pervasive developmental disorder not otherwise specified	<ul style="list-style-type: none"> • Applies to less severely affected children who do not meet criteria for either autistic disorder or Asperger's disorder

In medical, educational and social discussion, all of the above entities are often lumped together as “autism”, even though they can be very different conditions.

As mentioned above, the diagnostic criteria has steadily evolved and expanded over the past 30 years. A brief timeline is given here:

1943 – First published description by Leo Kanner

1980 – Autism first listed in the DSM as a separate disorder with specific diagnostic criteria (DSM III)

1987 – ASD expanded to include PDD-NOS (DSM III-R)

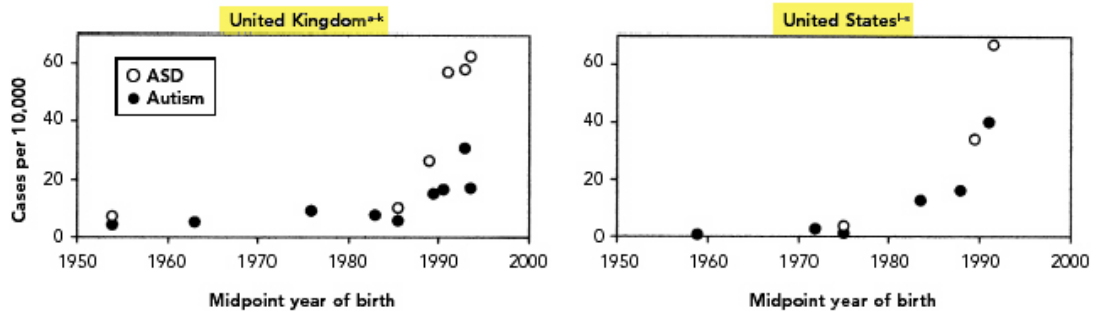
1994 – Autism diagnosis refined and Asperger's disorder introduced with specific criteria (DSM IV).

The expansion of the diagnostic criteria has gone hand and hand with an increasing awareness of the disorder among schools, clinicians and parents, resulting in greater acceptance of the diagnosis and an increase in autism-specific services and therapies available to children with ASDs.

Is there an epidemic of autism?

It is universally agreed that autism is being diagnosed at ever increasing rates in industrialized nations throughout the world, including the U.S., Canada, Denmark, Japan and Sweden. In the U.S., the estimated prevalence of childhood autism in 1950 was about 2-5 cases per 10,000 children; 2007 estimates increased to 60 per 10,000 (which is roughly 1 in every 150 children). A compilation of studies from the United States and the United Kingdom are shown below:

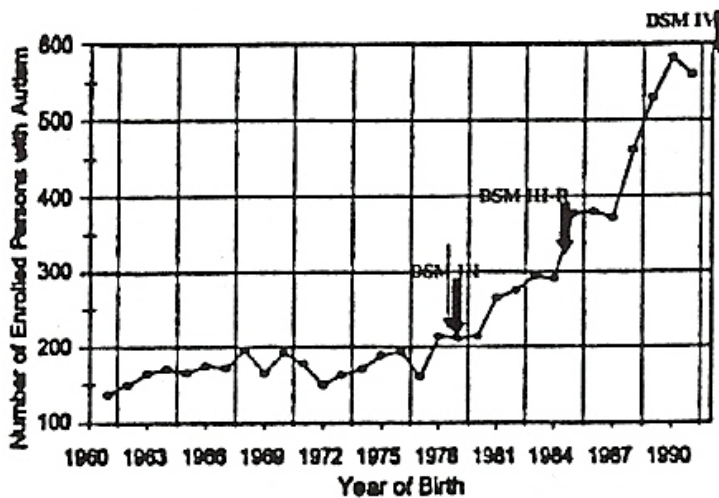
Figure 1. Reported prevalence of autism and autistic spectrum disorders (ASDs), by midpoint year of birth, United Kingdom and United States, 1954–1994



NOTE: These graphs show prevalence estimates from 11 U.K. and 8 U.S. studies. For studies with survey populations spanning a range of birth years, the midpoint of the birth year range is used.

If ten to thirty times more kids are now being diagnosed with autism, there has to be an epidemic, right? Many would say “not so fast.” There are several factors that might explain how many of the children currently being diagnosed with autism would have been given a different diagnosis in the past or else would have been missed altogether. Without question, the diagnostic criteria for autism spectrum disorders have expanded in the past 50 years, as detailed in the previous section. Prior to 1980, there were no formal, agreed upon criteria, and diagnosis was generally at the clinical discretion of the small number of child psychiatrists in the country. Up until the mid 1980s, statistical estimates of autism would only have included children with classic autism since PDD-NOS and Asperger’s were not officially recognized clinical entities. Each revision of the DSM has widened the diagnosis, producing more children who meet the criteria for an ASD without having an increase in the number of children who are actually affected. The following graph shows how the first revisions of the DSM criteria directly correlated with increases in diagnoses:

Figure 1 - Distribution of Birth Dates of Regional Center Eligible Persons with Autism



Modified from California Department of Development Services, 1999

A large autism population study from Canada actually subdivided cases by strict diagnosis. The following diagnosis rates were found:

Classic autism	22/10,000
PDD-NOS	33/10,000
Asperger's	10/10,000

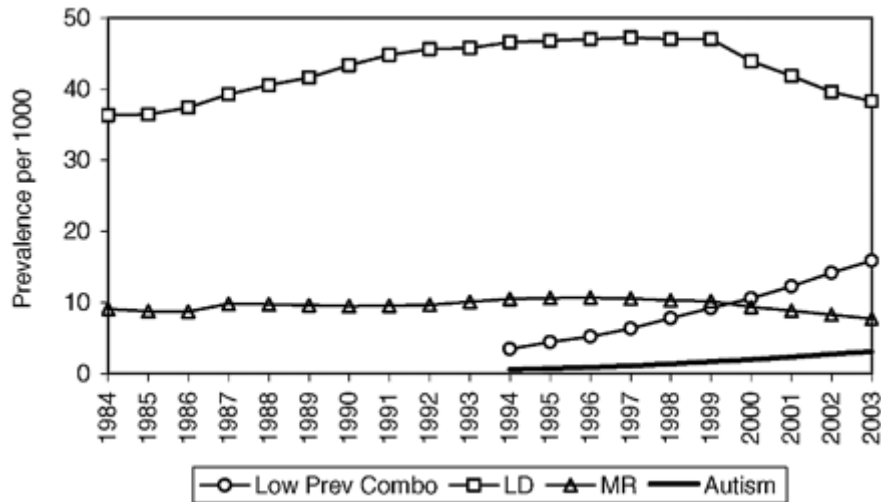
In other words, about two-thirds of the current ASD cases are not classic autism and would likely not have been included in earlier estimates of autism prevalence.

Further support of this concept of expanded diagnosis comes from a recent Finnish study. Children presently diagnosed with classic autism (not ASD) were re-evaluated using 1980 criteria; more than half of the subjects did not meet autism diagnostic criteria and, thus, would not have been diagnosed in the past.

The older understanding of autism specifically excluded children with known chromosomal syndromes such as Down Syndrome or Fragile X disease. We now know that as many as 10% of children with autism have alternations of chromosomal 15. Among these is Dr. Guetersloh's youngest daughter, Livia, who has a duplication of part of chromosome 15, causing seizures, global developmental delay and autism. In the past, children like Livia were not considered to be autistic because autism was understood as a disorder of altered attachment to parents, not a genetic, biological disorder. It is now recognized that many children with known chromosomal disorders have features that place them on the autism spectrum; these children are now benefiting from services specific to their autistic behaviors and are now being counted in the number of autism cases. Counting these cases has further expanded the reported prevalence of autism.

Putting all of this together suggests that **a large majority of children currently diagnosed with an ASD would not have received an autism diagnosis in the past.** Therefore, when looking at autism rates over time, comparing old and new studies is like comparing apples and oranges, so to speak.

Another phenomenon that can change the number of children noted to be diagnosed with autism without a change in actual cases is the process referred to as "diagnostic substitution". With diagnostic substitution, children with certain characteristics are seen as having a particular disorder at one point in time, but later children with the same characteristics are reclassified into a different diagnosis, changing estimates of prevalence without actually creating new cases. This occurs because there is often overlap between categories of developmental delays and disabilities. For example, many autistic children are also mentally retarded. There is evidence that many children with mental retardation, learning disabilities, speech delays and so called "other health impairments" who also have characteristics of PDD may now be primarily diagnosed and treated under an ASD diagnosis, whereas they were not in the past. This is illustrated below in a study compiling data from school districts around the U.S.



What this graph shows is that as more children are being treated with an autism diagnosis, fewer children are being treated for learning disabilities and mental retardation. While it's possible that the prevalence of some of these orders is truly changing, it's more likely that diagnostic substitution is changing the numbers between groups without any real difference in actual incidence. A child that was being treated and coded with mental retardation 20 years ago may be labeled as autistic today.

An Oxford study put this hypothesis to the test by reviewing a group of adults who were diagnosed with speech delay in childhood. What was found, after case review and interviews with the subjects' parents was that 12 of 38 speech delay cases reviewed would now be diagnosed as ASD (8 of those 12 with actual autism) using present day diagnostic criteria. These are actual cases, not a hypothetical group. This small study clearly demonstrates that diagnostic substitution is a real phenomenon, and it can account for a sizable increase in the incidence of autism without an actual autism epidemic. A larger review of children followed through the special education program in British Columbia concluded that at least one-third of the increase in autism cases from 1996-2004 was due to diagnostic substitution.

Finally, awareness of autism and the push for early diagnosis has greatly expanded as the evidence supporting the benefit of early intervention has grown. In 1991, the Individuals with Disabilities Education Act (IDEA) required school districts to provide educational services for all children. At that time, autism was added to the list of specific disabilities that were formally recognized. Suddenly, diagnosing a child with autism would actually be beneficial by making services available to them that were not available before. Along with autism, "traumatic brain injury" was also recognized under IDEA and by 2000 the number of children treated under this code rose by 50 times. Nobody would suggest that there were actually 50 times more children with traumatic brain injury, they were just starting to receive more services through the educational system.

The standard of care for general pediatricians has changed over the past decade and now includes formal developmental screening at several ages in early childhood in order to identify children with developmental differences as early as possible and get them

services. This is very much a new phenomenon. It stands to reason that if you are looking for something, you are more likely to find it.

This idea is supported by data from California and Texas school districts which shows that autism is more frequently diagnosed in higher income school districts. The map below shows the number of autism cases in different districts in the Los Angeles area. Given the close geographic proximity, it is likely that environmental exposures are similar. Access to medical care and parental education, however, are not similar. The poorest school district, South Central LA, has the lowest autism numbers, revealing that factors other than just disease incidence affect the reports of the prevalence of autism.



Overall, it is our opinion that expanded diagnostic criteria, diagnostic substitution and increased autism awareness and available services are the biggest factors increasing the reported prevalence of autism spectrum disorders.

Known Causes of Autism

Is this the whole story? Maybe, maybe not. It seems that expert opinion differs on whether or not, after all of the above factors are considered, there is still an actual increase in the number of children affected by ASDs. There certainly is not the raging epidemic that would be suggested on the surface by reports of 30-fold increases, but there could still be a subtle increase that is hidden beneath the diagnostic issues we've already reviewed. To better evaluate the purported theories of the possible causes of an increasing rate of ASD cases, it is necessary to first look at what is already known about the causes of autism spectrum disorders.

Autism is felt to have a strong genetic basis with features first present very early in life in most cases. Evidence for this statement comes from several lines of investigation. Twin studies have revealed that if one identical twin has an ASD, there is a 90% chance that the other twin will also be affected. If the twins are non-identical, however, the risk drops below 10%; the 90% rate between monozygotic twins (who share identical DNA) is much higher than most other complex disorders that are known to be influenced by genetics, like asthma or ADHD. Home video studies have shown detectable abnormalities in autistic children as early as two months of age. About 10% of autistic cases have known specific gene or chromosomal associations, with more seemingly discovered everyday. Most of these known causes are chromosomal deletions or duplications. Finally it has been noted that both advanced maternal and paternal age increases the risk for autism-affected offspring by a factor of 2 to 6, depending on the study.

THE AGE FACTOR

Risk of having a child diagnosed with autism by age 10:

Age	Father: 1 in ...	Mother: 1 in ...
Under 20	387	251
20-24	203	182
25-29	176	156
30-34	154	149
35-39	128	130
40-plus	116	123

Source: *Archives of Pediatrics & Adolescent Medicine*

This age association is most likely due to increasing chromosomal changes in our eggs and sperm as we age, as is seen in disorders such as Down Syndrome. It's even possible that this effect could amplify with multiple generations of older parents. It is also possible, however, that other factors related to a parent's age, such as family income, access to medical care and, possibly even, attentiveness to behavioral issues may provide non-genetic explanations for the noted associations.

Those who feel that autism is truly on the rise suggest that there must be an environmental trigger. Isolated autism cases have been traced to pregnancy exposure to thalidomide, valproic acid and maternal rubella infection. Thalidomide was used to treat morning sickness in the 1950s and 1960s before it was causally linked to multiple severe birth defects and was taken off of the market. Interestingly, only those thalidomide-exposed infants who had abnormalities with their ears, but not their limbs, were found to have autism. This is important because the ears develop much earlier in gestation than the arms and legs, suggesting that the crucial time for the autistic wiring of the brain must be early in pregnancy. Maternal rubella infection has also been associated with autism, but only if the infection occurs in the first or second trimester of pregnancy. The irony should not be lost: rubella vaccination of children (part of the MMR vaccine) actually *prevents* autism by decreasing the spread of rubella infection to pregnant mothers. Looking at these known exposures, it seems likely that other environmental factors, if they exist, would have their effects during the early phases of pregnancy and not after birth.

Based on the above findings, including the strong genetic associations, the evidence of autistic signs early in infancy and the only known environmental causes being active during early pregnancy, it is our opinion that autism is rarely, if ever, due to postnatal environmental factors.

VACCINES AND AUTISM

This finally leads us to the question of vaccines as possible environmental “toxins” that are responsible for causing new cases of autism. The main focus of the argument is that the vaccine schedule in this country has significantly expanded in the past thirty years as we have found ways to prevent more life-threatening diseases; this expanded shot schedule coincides in time with the increasing diagnosis of autism. Basically, what’s suggested is that more shots equal more autism. We will review the specifics below. In the meantime, it is key to keep in mind that a temporal relationship (two things occurring at the same time) does not make a causal relationship (one of those things is actually responsible for causing the other). As an example, home computers first became available in the 1980s and are now present in almost every home in the country; however, it is unlikely that PCs are responsible for autism.

MMR and Autism

The first vaccine to receive widespread attention with regards to autism was the combination measles-mumps-rubella or MMR vaccine. As the name implies, this vaccine immunizes against 3 separate infections. It does this by using ‘attenuated’ or weakened versions of the three viruses. The purpose of the 3-in-1 combination is to decrease the number of shots children need to get the same immunity.

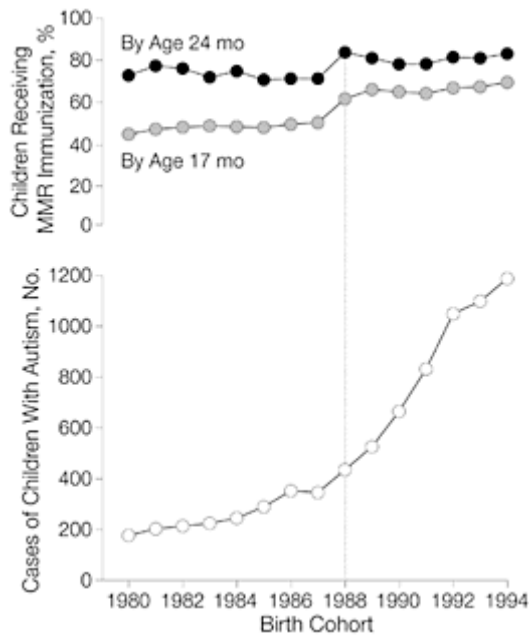
In 1998, Andrew Wakefield, a British gastroenterologist, published a case series including 8 patients with autism where he suggested that their developmental delay was triggered by the MMR vaccine. “The Wakefield Hypothesis” suggests that certain genetically predisposed individuals will develop persistent intestinal measles infection after MMR exposure, leading to a “leaky gut syndrome” that allows molecules from the GI tract (natural or environmental toxins) to enter the circulation and cause brain damage

leading to a regressive form of autism. This single, small case series and its' 2002 follow-up paper from the same group created widespread mistrust in the MMR and vaccination in general and spurred the development of a whole area of fringe practices based on special diets and other GI manipulations.

A detailed review of the technicalities of this paper and the research that has followed is beyond the scope of this discussion, but a few points are in order. First, Wakefield's hypothesis makes little sense, since natural measles has never been associated with autism, even in the most severe cases of measles encephalitis. It would be strange for the weakened form of measles that comes in the vaccine to cause a type of brain damage that has not been identified with the more virulent natural infection. Second, a thorough investigation of Dr. Wakefield's research has revealed unethical behavior. The British General Medical Council ruled in 2010 that Dr. Wakefield acted "dishonestly and irresponsibly" in the publication of his study and removed his license to practice medicine. **10 of the 13 original authors of the Wakefield paper had already retracted their names post-publication** (an extraordinarily rare occurrence) and the publishing journal, The Lancet, had already issued a "Statement by the Editors" reporting an undeclared conflict of interest between Dr. Wakefield and a trial lawyer who was trying to build a personal injury-autism case. **The journal formally retracted the paper** (again, extraordinarily rare for a medical/scientific journal) after the GMC ruling. Wakefield actually received \$800,000 to provide evidence that the MMR caused autism, a compromising conflict that was not disclosed when the study was submitted for publication. A research assistant in his lab, working on this project, testified that all of the positive results in his study were proved to be false positives, and this was known prior to publication of the paper. Pathology reports that were noted to be abnormal by the study's authors were previously judged as normal by the hospital pathologists. An independent review of the medical records of the patients in the study contradicted the reported histories in the paper. Finally, an independent, multi-national attempt to repeat his exact experiment showed no evidence of measles virus in the intestines of autistic children with GI disturbances. Overall, the Wakefield studies have been completely discredited in the scientific community for lack of blinding, inappropriate controls and evidence of outright fraud. Details about the Wakefield paper and the following investigation are available online at www.briandeer.com/mmr/lancet-summary.htm.

Despite the lack of scientific evidence, the Wakefield articles lit a wildfire of public concern about the safety of the MMR vaccine and shifted the perceived burden of safety proof back to the medical community. It is impossible to prove that one thing doesn't cause another, but the case against the MMR as a major cause of the rising autism rates falters under close evaluation. Let's take a look at some of the evidence.

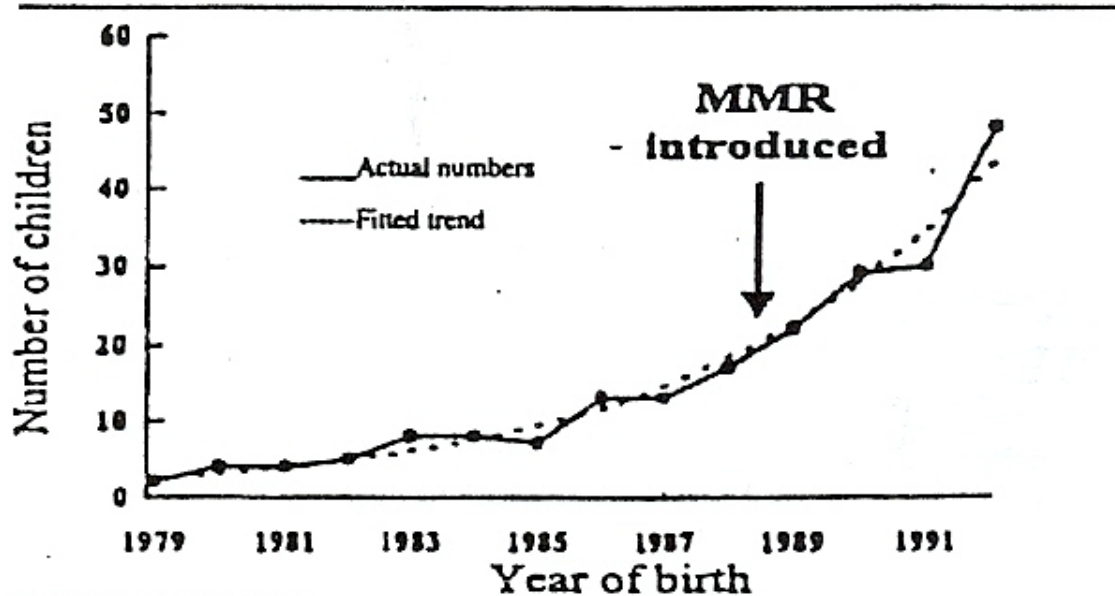
In the U.S., the MMR vaccine was first licensed in 1978 and quickly saw large scale use (who wouldn't want to give their kids one shot instead of three?). MMR vaccination has been widespread with stable rates for over twenty years. The graph below shows that rates of autism continued to increase well after MMR vaccination rates were very stable.



If the MMR vaccine was largely responsible for the rise in autism, we should have seen a sharp rise after it was introduced, with a big surge of cases in the early 1980s, followed by a leveling-off in the rise after vaccination rates stabilized (by the late 80s and early 90s). Instead, children born in 1988 and 1994 had similar rates of MMR vaccination rates at similar ages, but the 1994 group had three times as many autism cases.

A separate case study comes from the United Kingdom where the MMR vaccine was not introduced until 1988. The graph below shows that autism was already on the rise before MMR was available.

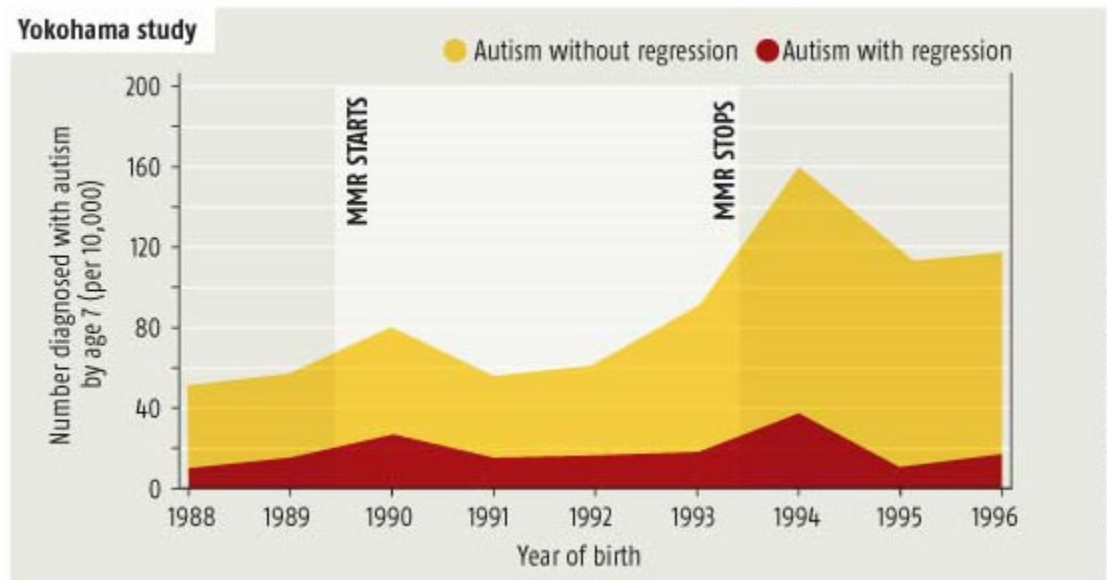
Cases of autism under 60 months of age in North East London by year of birth



Taylor B. et al. Lancet 1999

This data suggests that autism in England does not correlate with MMR use. Not included in this data is the lack of a drop in autism cases after MMR vaccination rates dropped with the publication of the Wakefield papers.

A final critical example comes from the experience in Japan. Like England, Japan introduced the MMR in 1989; however, the MMR vaccine was recalled in 1992 after safety concerns regarding cases of aseptic meningitis (a complication due to the mumps component of the Japanese MMR, a side effect not seen with the U.S. vaccine). No child has received the MMR vaccine in Japan since 1993. The measles, mumps and rubella vaccines are given individually, each separated by at least one month. So, if MMR causes autism, Japan should have seen a steep rise with the MMR introduction followed by an equally steep decline after withdrawal. The graph below shows what actually happened.



Children born after 1993, all receiving separate measles, mumps and rubella vaccines, were more likely to be diagnosed with autism than the children born between 1989 and 1993 when MMR vaccine was in use (with maximum vaccination rates of 82% in 1991).

Putting together the experience from these three different countries with different MMR vaccination programs, we see a continual increase in autism diagnosis in all three areas unrelated to the introduction, discontinuation or routine use of the MMR vaccine. After reviewing the available evidence, the Institute of Medicine (which will be discussed in more detail at the end of this review) concluded the following in 2004: “the epidemiological evidence favors a rejection of the causal relationship between the MMR vaccine and autism. In addition, the committee recommends that the funding for autism research be channeled to the more promising areas.”

It is the opinion of our practice that MMR vaccination is not a cause of autism, separate vaccines do not provide any safety benefit, and children should be routinely immunized after their first birthday to prevent these potentially serious diseases.

Mercury and Thimerosal

Thimerosal is a trace component found in some vaccines that has been suggested by some to cause autism. Thimerosal is an ethyl-mercury-containing preservative that has been used in vaccines since the 1930s. Methyl-mercury can be an environmental neurotoxin when ingested in large quantities. As the “mercury causes autism” theory goes, the addition of Hepatitis B and Hib vaccines to the routine immunization schedule in the early 1990s increased an infant’s potential mercury exposure from vaccines in the first six months of life from 75 micrograms to 187.5 micrograms, and this rise was responsible for the rising rates of autism. The theoretical possibility of harm from mercury in the vaccines led the American Academy of Pediatrics and the U.S. Public Health Service to recommend removal of thimerosal from the routine vaccines in 1999; the only regularly administered infant vaccine that now contains thimerosal at anything

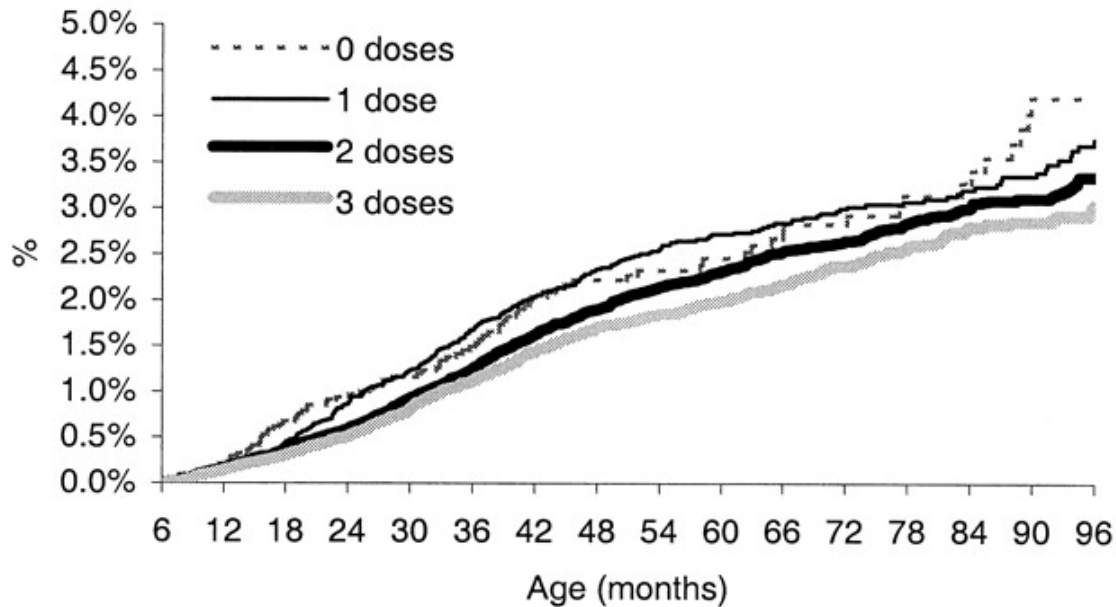
above trace levels is the flu vaccine (although there are some flu vaccines that do not contain thimerosal). It bears noting that a common theme in anti-vaccination circles is that pharmaceutical companies have corrupted government agencies and physician groups, and together they have conspired to mislead the public; yet, it was these very organizations, namely the AAP and CDC, that recommended thimerosal removal long before there was a loud public outcry concerning mercury exposure.

If mercury is indeed a neurotoxin, the amount in the vaccines increased as autism diagnoses increased, and even the AAP wanted it taken out of the vaccines, then that's our environmental trigger, right? Well, not exactly. A plausible hypothesis doesn't cut-it as scientific evidence or proof. The mercury hypothesis has a few holes to examine before we actually look at the evidence regarding vaccines.

Mercury does damage brain cells, but even with the highest observed levels of environmental contamination, it has not been associated with autism. The largest study of the toxic effects of mercury comes from Iraq where a heavily contaminated grain supply caused widespread mercury poisoning, killing 450 people. Follow-up of this incident showed that children who were exposed to high mercury levels during pregnancy suffered from developmental delays, but not autism. Furthermore, thimerosal contains ethyl-mercury while most environmental mercury is methyl-mercury. Methyl-mercury is what has actually been studied and used to determine safe versus toxic environmental exposures. Ethyl, methyl, doesn't sound like there's a whole lot of difference, but there is for our bodies. Ethyl-mercury clears from our body much more rapidly and is less likely to accumulate in brain tissue when compared to methyl-mercury because it is much more water soluble. Toxicology data based on methyl-mercury, therefore, exaggerates the actual risk from thimerosal. So, thimerosal may not be nearly as bad as the more common environmental mercury, and even that has never been shown to cause autism despite episodes of major toxic exposures.

That all sounds good, but is it safe in vaccines and can we show that it didn't cause autism or developmental delays when injected during immunization? Once again, you can't prove a negative association, but the evidence is pretty convincing. Studies from the U.S, the U.K., Sweden, Canada and Denmark, all comparing thimerosal-exposed and unexposed populations have revealed the same thing: thimerosal exposure doesn't increase the risk for autism or developmental delays. One example is given below. This study, from the United Kingdom, looked at multiple developmental and psychiatric diagnoses given to children to see if there was a relationship with the amount of thimerosal exposure in the first 4 months of life. What you see is no significant difference in developmental outcomes whether children receive 0 to 3 doses of thimerosal-containing vaccines. This held true for all outcomes measured.

General developmental disorders



The most telling test for the “mercury causes autism” hypothesis comes from countries like Denmark, Canada and the U.S. where thimerosal has been completely eliminated or drastically reduced. As noted above, no vaccines given routinely in the U.S. before 6 months of age have thimerosal, and that has been the case since about 2002. The flu vaccine can first be given at six months, and some flu products still contain thimerosal. The dramatic drop from a maximum exposure of 187.5 micrograms of mercury down to a maximum of 25 micrograms in the first six months was hypothesized to have a significant impact, specifically on autism diagnoses. To quote a leading advocate of the mercury hypothesis, David Kirby, author of *Evidence of Harm*, “if the total number of 3 to 5 year olds in the California DDS system has not dropped by 2007 that would deal a severe blow to the autism-thimerosal hypothesis.” Well, guess what? The results are in and autism hasn’t gone away. In fact, diagnoses have continued to increase despite the dramatic reduction in mercury exposure. As noted above, the same thing has been experienced in Canada, Sweden and Denmark. Thimerosal removal has not dented the autism prevalence.

Despite the evidence, the anti-vaccinationists have continued to confuse the debate by clamoring away with lines like “there’s still thimerosal in 11 vaccines.” The reality is that mercury exposure from vaccines is down to the levels used in the 1980s immunization schedule when autism was much less common. According to the Institute of Medicine, “the committee concludes that the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.”

It is the opinion of our practice that thimerosal in the vaccines does not contribute to autism or developmental delays and the lack of benefit seen from removal of mercury from the routine vaccines should caution us when reviewing other claims about “toxins” in vaccines.

Vaccines and the Immune System, Is It Too Much?

Another often stated concern about vaccines is that too many can “overwhelm” the immune system. This fear is tapped by the catch-phrase “too many, too soon.” This argument suggests that too many vaccines given at the same time to a young infant without a fully developed immune system causes harm, possibly including brain damage. Once again, the rise in the diagnosis of autism coinciding with the expansion of the vaccine schedule is offered as “proof” to validate this idea. To see if this fear has merit, it’s necessary to review some immunology.

The basic element that our bodies recognize when mounting an immune response is termed an antigen. Antigens come in multiple forms; for infectious agents they most often are proteins that are usually on the surface of bacteria, viruses, parasites or fungi. Most infectious agents present our bodies with many different antigens. Each antigen leads to the production of an antibody (the so-called one antigen, one antibody theory); antibodies remain in our blood and serve a memory function, ready to activate the immune system if they encounter their respective antigen in the future. Vaccines work by presenting antigens to our immune system, leading to the production of protective antibodies. Ideally, the vaccines trigger an antibody response without making us sick.

Vaccines can be made by taking a bacterium or virus and weakening it in the lab through a process called attenuation. Most of the earliest vaccines, like small pox, live polio and whole cell pertussis, used attenuated strains to provide immunity without illness. Newer technology has led to the production of ‘cleaner’ vaccines that isolate one or several crucial antigens from the bacterium or virus and use these alone to trigger our protective immunity. These single antigen vaccines provide enough of a fingerprint for immune recognition and protection from disease with much less overall immune stimulation because they reduce the overall number of antigens contained in each vaccine.

The table below compares the relative antigen stimulation from the routine vaccine schedule over several time periods. It clearly shows that **even with more vaccines, the number of antigens, and therefore the degree of immune stimulation, is actually decreased with the modern vaccine schedule.** How’s that possible? The Hepatitis B, Hib, Prevnar, IPV and DTaP vaccines use single antigens instead of whole cell bacteria or live viruses. The key is that the number of vaccines and number of shots does not equal the number of antigens or amount of immune stimulation. Therefore, the concept of “overwhelming the immune system” doesn’t really make sense when applied to current immunization practices.

Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines Over the Past 100 Years

1900		1960		1980		2000	
Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins/Polysaccharides
<u>Smallpox</u>	<u>~200</u>	Smallpox	~200	Diphtheria	1	Diphtheria	1
Total	~200	Diphtheria	1	Tetanus	1	Tetanus	1
		Tetanus [‡]	1	WC- Pertussis	~3000	AC-Pertussis	2–5
		WC- Pertussis	~3000	Polio	15	Polio	15
		<u>Polio</u>	<u>15</u>	Measles	10	Measles	10
		Total	~3217	Mumps	9	Mumps	9
				<u>Rubella</u>	<u>5</u>	Rubella	5
				Total	~3041	Hib	2
						Varicella	69
						Pneumococcus	8
						<u>Hepatitis B</u>	<u>1</u>
						Total	123–126

In actual practice, this is put to the test whenever new vaccines are added to the schedule. New vaccines must be given along with the existing vaccines and observed for safety before licensing approval. For example, the pneumococcal conjugate vaccine, known as Prevnar, was given to over 17,000 children along with DTaP, Hib and IPV and side effects and reactions were compared to over 17,000 children receiving those 3 vaccines plus a control vaccine. All 35,000 children were observed for 5 years before Prevnar was approved for use. It is important to realize that this is standard testing as the vaccine schedule expands.

A 2010 retrospective study looked at neuropsychological outcomes in children who received all of their vaccines on schedule compared to children who had their vaccines ‘spread out’ or did not receive all of their vaccines. Children fully vaccinated on schedule, including multiple vaccines at a time when indicated, had no adverse neurological outcomes; they actually tested better in almost all analyses performed.

It is our practice's opinion that the administration of immunizations following the standard recommended schedule does not overstimulate the immune system and separating out vaccines offers no safety benefit.

Aluminum – The “New Thimerosal” Really?

A relatively newer area of focus for anti-vaccination groups is Aluminum. Aluminum is an adjuvant, a substance added to a vaccine in order to stimulate a greater immune response. Adjuvants help immunity to develop with lower antigen levels delivered in fewer doses, i.e. fewer shots. A discussion of how aluminum enhances immunity is beyond this review, but this property has been known and manipulated for a long time; aluminum has been used in vaccines for over 75 years. Aluminum is receiving greater scrutiny as the MMR and mercury theories are losing credibility. Why aluminum? Let's take a look.

Aluminum is the most abundant element in the earth's crust, and it is ingested daily by babies from many sources, including both breast milk and formula. Aluminum is poorly absorbed after ingestion, so most of it harmlessly passes out of the body, but a small level does remain. Aluminum can also enter the body from IV medications and fluid solutions, but it is usually excreted by the kidneys without any problems. People who have altered kidney function, like dialysis patients and premature babies, may be less effective at removing aluminum, and some have been shown to suffer toxicity of their central nervous system (although not autism) from persistently high blood aluminum levels. Toxicity has been reported at serum concentrations of 100 micrograms per liter and it is possible that toxicity could occur at even lower levels than this.

Robert Sears, a California pediatrician and author of The Vaccine Book, has raised the question “is aluminum the next thimerosal”? The implication is that aluminum exposure has gradually increased over the years with the vaccine schedule; it is possible that there could be a toxicity that has gone unrecognized. To support this idea of vaccine-induced aluminum toxicity he presents a series of calculations comparing the known toxic levels in patients receiving continual intravenous solutions containing aluminum to the amount of aluminum injected with the vaccines. Low and behold, he reports that the aluminum in the vaccines surpasses the levels that have been shown to be toxic. He goes on to call for new research into aluminum safety and recommends an alternative shot schedule that gives no more than one aluminum-containing vaccine at a time.

Scary sounding stuff indeed, especially coming from a pediatrician who generally advocates that children be vaccinated. There's only one problem: there is a world of difference between the accumulation of aluminum throughout the body from continuous IV infusions versus injected doses separated by the course of weeks to months. The real value to examine to compare these two different aluminum exposures is known as the “total body burden” which represents how much aluminum actually remains in the body after an exposure regardless of the source. When aluminum is given as an injection, the majority of it is rapidly removed from the body; over 50% is eliminated in the first 24 hours. The aluminum that remains will distribute to several tissues with the following preferences: kidney > liver > heart > lymph > brain. This total body burden can be estimated by mathematical models based on the known properties of aluminum excretion.

The following figure shows the effect on total body aluminum when injected from vaccines compared to ingestion from breast milk or formula.

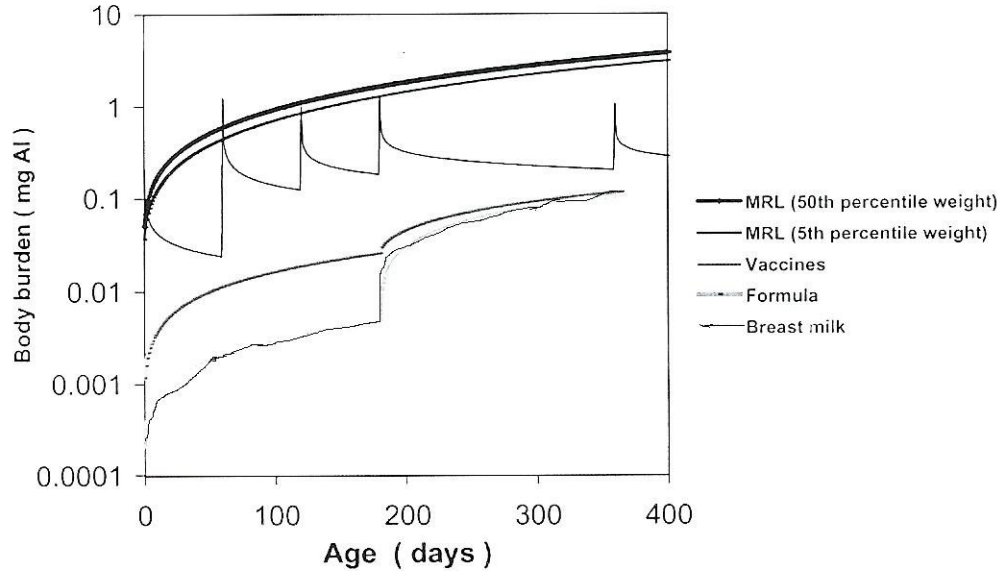


Fig. 1. Aluminum body burden contributions from diet and vaccines relative to MRL level intake.

The top lines in the graph reflect body burden levels after ingestion of the minimal risk level (MRL) for aluminum toxicity established by ATSDR (the Agency for Toxic Substances and Disease Registry). The ATSDR MRL is calculated from studies in mice fed various levels of aluminum and observed for toxicity. The lowest observed toxic levels were above daily ingestion of 62 mg/kg body weight/day. To adjust for possible species differences and variations between individuals (correcting for the possibility that some people have more problems excreting aluminum or more sensitivity to toxic effects than others) this level has been divided by a factor of 30 to come up with a minimal risk level of 2 mg/kg/day of oral aluminum ingestion. The mathematical model alluded to above calculates how much aluminum remains in the body after oral ingestion so that we can compare it to the effect of periodic aluminum injection. The results, shown above, indicate that after a very brief peak on the day of injection, the sustained total body aluminum remains below the conservatively estimated minimal risk level.

A couple of details about these calculations are worth mentioning. The referenced data did not factor the effect of aluminum from Prevnar or Hepatitis A, both of which contain some aluminum. Inclusion of these vaccines would not change the conclusions for patients in our practice because the amount of aluminum in the vaccines used in our office (specifically the DTaP), is significantly less than the amount used in these calculations (which assumed maximal possible aluminum of the available vaccines).

Additionally, it is worth comparing the ATSDR MRL obtained from mice studies to the known toxicity in humans. As mentioned above, the American Academy of Pediatrics references a blood aluminum concentration of 100 micrograms/L as the known

toxic level in children. A 1991 study of infants taking aluminum-containing antacids for at least 4 weeks at an average amount of 123 mg/kg/day had blood aluminum levels of 34 micrograms/L. That's right, infants (average age 6 months) consuming 60 times more aluminum than the suggested MRL had blood levels that did not reach the known toxic levels. It should be noted that there was no observed toxicity in these infants, although long term follow-up was not provided. Remember that the body's aluminum levels from vaccines falls below the 2 mg/kg/day ingestion level. That leaves an **overwhelming margin of safety for the level of aluminum in vaccines as it relates to known toxic doses.**

The evidence regarding safety of aluminum in the DTP vaccine, one of the largest sources of aluminum in vaccines, was reviewed by the Cochrane Collaboration in a 2004 meta-analysis of all of the published safety studies. The Cochrane group is an international organization that studies worldwide health issues and publishes evidence-based reviews; their reviews are considered the gold standard for evidence-based evaluations by the medical community. Their conclusion, based on the available evidence and the 70 year history of usage of aluminum in vaccines was that "we found no evidence that aluminum salts in vaccines cause any serious or long-lasting adverse events.....we do not recommend that any further research on this topic is undertaken". This statement is supported by the study of DTaP exposure and developmental outcomes discussed in the Thimerosal/Mercury section above. As was noted, developmental outcomes were no different whether infants received 0, 1, 2, or 3 doses of aluminum-containing DTaP in the first 4 months of life. This study was designed to look at mercury exposure, but it also reflects aluminum exposure since there were not any other aluminum-containing vaccines routinely used in England during the study period.

So, is aluminum the new thimerosal? Remember the previous discussion exonerating thimerosal in vaccines as a cause of toxicity, specifically as it relates to autism? Hopefully history does not have to repeat itself with misinformed worries, ineffective "therapies" and research dollars to disprove this false therapy as well.

It is the opinion of our practice that the amount of aluminum in vaccines is many times below the harmful level, and that there is no benefit to avoiding or spreading-out aluminum-containing vaccines.

Mitochondria – Proof That Vaccines Cause Autism?

The 2008 Federal vaccine court decision to award damages to the family of Hannah Poling has provided a new angle to the vaccine-autism debate. Hannah Poling is a little girl diagnosed with a mitochondrial disorder which includes global developmental delay and autistic features. The vaccine court (in place to compensate individuals in the rare cases of significant adverse events actually caused by vaccination) ruled that she had a pre-existing disorder of her mitochondria which was stressed when she developed fever after receiving vaccines at 19 months of age, and this event may have triggered damage leading to her developmental issues. Many have jumped on the bandwagon with claims, among other things, that vaccines cause normal mitochondria to malfunction or that there

is a significant population of children with undiagnosed mitochondrial disease who get worse after vaccinations and go on to develop autism.

What's going on here? A brief cell biology review is necessary to make sense of this issue. Mitochondria are like little energy banks within all of our cells. They convert energy from carbon chains into a molecule called ATP that can provide an immediate energy source for all of our cellular processes. Think of them like a bank where you can take a check and get cash for immediate spending. Some people have malfunctioning mitochondria which can't generate the energy when their cells need it, like a bank with a broken ATM machine that can't give out cash. During times of stress, as occurs with a fever or an infection, the mitochondria have to work overtime to meet our bodies' needs or else cells will malfunction or shutdown due to their energy shortage. When children have malfunctioning mitochondria, they often present with "stroke-like" events triggered by episodes of increased metabolic demands. These metabolic crises result in neuron death and successive loss of function injuries to the brain.

According to the vaccine court, Hannah Poling's brain was possibly damaged because her mitochondria couldn't respond to the stress caused by the fever she developed after she received several vaccines on the same day. Based on the standard of "biological plausibility", the above sequence of events could have happened, prompting the court to award damages. It should be noted that there is no proof that this is actually what caused her developmental regression, but only presents a plausible argument. Presumably, other causes of fever, like the flu, chicken pox or any other common infection, could have presented the same mitochondrial crisis and triggered the same net effect on her brain. Most experts have argued that similar children are still far better off receiving vaccines as opposed to being left susceptible to the more severe stresses and possible regressions caused by the natural infections they prevent.

Despite the attempts by some to generalize the Poling case to suggest a significant vaccine-autism link, mitochondrial diseases affect a much smaller number of people (estimated 1:4000) than have been noted to have autism spectrum disorders (estimated 1:150). According to the United Mitochondrial Disease Foundation (UMDF), "there are no scientific studies documenting that childhood vaccinations cause mitochondrial diseases or worsen mitochondrial disease symptoms; in the absence of scientific studies, the UMDF cannot confirm any association between mitochondrial disease and vaccines". It is known that mitochondrial diseases are caused by mutations in the mitochondrial DNA and not environmental exposures.

Even though many details of the Poling case remain in debate, particularly since the family has not released the complete medical record and they actually have disputed the basis of the court's settlement in their favor, all of the available evidence points to Hannah Poling's case being at most a rare exception and not a new, generalized rule regarding harm from vaccines.

It is the opinion of our practice that mitochondrial diseases do not present a common risk for vaccine safety and the decision in the Hannah Poling case should not impact routine vaccination decisions for otherwise healthy children.

What About All of Those Preservatives?

Many other ingredients involved in vaccine production have been put forth on lists of scary sounding “toxins” included in vaccines. Below is a summary of other vaccine ingredients from Pharmaceutical Research and Manufacturers of America.

Facts About Childhood Vaccine Ingredients

Groups challenging the safety of immunizations have raised allegations that certain Food and Drug Administration (FDA) approved ingredients in vaccines are “toxins.” In many instances these allegations are completely incorrect. In others, the claims are taken out of context.

Toxins are typically defined by dose or level of exposure. Even something as benign and essential as water can be toxic if consumed in large quantities. Another example is chlorine, which can be a highly toxic chemical and was used as a weapon in World War I. Yet small amounts of chlorine are present in the tap water we drink every day. Without that chlorine, tap water would not be safe to drink.

Vaccines are extensively tested and highly regulated products. Prior to their approval by FDA for use in the market, vaccines are required to undergo significant clinical trials. These trials test the safety of all components in a vaccine. Tests are first conducted in adults and then in older children; only when safety has been demonstrated in these populations is the product then tested in young children.

Vaccine trials are rigorous and usually take many years to complete to obtain FDA approval. As examples, the recently approved vaccines for rotavirus had 70,000 children in clinical trials and the pneumococcal conjugate vaccine had close to 40,000 children.

New vaccines are evaluated for their effects in the presence of existing vaccines. Vaccines being tested in clinical trials – especially in children – are given in conjunction with vaccines already on the market. To withhold existing lifesaving vaccines from a group participating in a clinical trial would be unethical as it would leave that group of children exposed to serious infectious diseases. Moreover, this ensures compatibility and safety when given along with the other vaccines.

Below is factual information related to the myths perpetuated about vaccine ingredients:

Formaldehyde

Formaldehyde can be used as an antimicrobial. Formaldehyde effectively inactivates the organisms and biological substances used in vaccines. Formaldehyde is present in the environment and is a byproduct of metabolism so it is already present in the human body.

Antifreeze

There is no antifreeze in vaccines. The active ingredient in antifreeze is ethylene glycol which is toxic to ingest. A single additive of some antifreeze – polyethylene glycol – is used to inactivate the flu virus in one brand of that vaccine; it is also used in the purification of certain vaccines. This chemical is also widely and safely used in personal care products, such as skin creams and toothpaste and is safely consumed in large, daily quantities in the laxative Glycolax (MiralaxTM).

Claims have also been made that various substances used to support the growth of viruses used in vaccine preparation are present in the final vaccine product. This is untrue and is akin to saying there are trees in apple juice just because the apples originated on trees. In the case of vaccines, viruses are grown initially in cell lines of various types. Then, the viruses are harvested and go through multiple processing and purification steps over months of time before the final product is ready for use.

Below are facts about the specific allegations raised:

Aborted Human Fetus Cells

Vaccines do not contain human cells or tissue. Human cell lines are used in the early stages of production of some vaccines because viruses need a living cell in which to grow. These cell lines were derived from fetal tissue more than 40 years ago. The same two cell lines are reproduced and used repeatedly so that no new fetal tissue is required in the ongoing production of vaccines. As with all viral vaccines, multiple purification steps ensure that cells are not in the final vaccine product.

Chick Embryos

There are no chick embryos in vaccines. Many influenza vaccines begin with viral growth in chicken eggs and then undergo multiple purification steps. Some residual egg proteins may be present in the final vaccine product. Chicken eggs and their proteins are routinely consumed as part of the human diet.

Monkey Kidneys

There are no monkey kidneys in vaccines. Monkey kidney tissue is used to support the growth of certain viruses for making vaccines; for example, it was used to support the growth of the weakened polio virus that went into the oral polio vaccine. Multiple purification steps ensure that no kidney cells are present in the final product.

Fetal Bovine Serum

When viruses are growing in cells, they need a source of nutritional ingredients. In some instances fetal bovine serum is the source of these growth factors. Once the viruses are

harvested, they undergo multiple processing and purification steps before the final product is released to the market.

It is the opinion of our practice that the adjuvants, preservatives and trace biological products in vaccines do not cause any significant health concerns. Avoiding, delaying or separating vaccines based on these ingredients is of no benefit.

CLOSING

Hopefully this review gives you an adequately detailed look at the issues regarding autism and vaccine safety and explains our confidence in recommending that parents follow the American Academy of Pediatrics and Centers for Disease Control routine immunization schedule. We appreciate the fear that parents must face from the heartfelt protests of those that feel that vaccines pose excessive risks to the development and well-being of their children. The only way to deal with this fear is with an unbiased review of the scientific data using accepted principles of medicine. When reason disproves the basis of these concerns, then we must move on or else we allow ourselves to be controlled by irrationality. As your pediatricians, we are not just doctors, but also parents. We vaccinate our own children by the recommended immunization schedule; even Dr. Guetersloh's daughter, who has autism, is vaccinated on schedule, without hesitation.

People have called for Congress to intervene and demand a review of our national immunization practices. This is repeating history as the CDC and NIH did just this in 2001 when the Institute of Medicine was asked to conduct an independent review of vaccine safety, specifically as it related to autism. The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The National Academy of Sciences is comprised of the finest scientists in the nation. Think of them as the "Academy Award" winners of their field. Their final independent review was published in 2004, and as discussed above, they concluded that there is sufficient data to rule-out a vaccine-autism link and recommended further research dollars spent elsewhere. This is not a trivial point, a group of the finest scientists in our country, independent of pharmaceutical company interest, ruled convincingly on the side of vaccine safety. We don't need more studies, we need to listen to the science.

The vaccine-autism debate has even had its day in court. In 2008, the U.S. Court of Federal Claims, reviewed the vaccine injury claims. Over 5,000 petitioners had made claims to the National Vaccine Injury Compensation Program (VICP). Three of the best cases were chosen to be heard and all three cases were soundly rejected by three different judges after extensive review of medical expert testimony, expert reports and scientific publications; this even though the vaccine court applies a lower standard for proof than a typical federal or civil court. George Hastings, a Special Master judge that reviewed one of the petitions, stated in his decision, "This case...*is not a close case*. The overall weight of the evidence is *overwhelmingly* contrary to the petitioners' causation theories...

Does that mean that there is no risk to vaccinating? Absolutely not. However, no human endeavor comes with zero risk. Children tragically die every year playing baseball, but no one suggests that we shut down America's pastime. The risk is so small that it doesn't outweigh all of the great benefits. Likewise, serious vaccination risk is extremely small, and the benefit is far greater than just playing a baseball game.

This review has focused on risks while ignoring the subject of benefit. A detailed listing of the benefits of each vaccine can be obtained in our office from the Vaccine Information Statements available for each vaccine. We will briefly discuss measles here as a small example of the importance of immunization.

Measles is an extremely contagious disease. It was widespread in this country before the availability of routine immunization, and it is still prevalent throughout the world, accounting for an estimated 252,000 deaths in 2007. Prior to the 1963 introduction of the vaccine in the U.S., there were a reported 500,000 measles cases per year with 4,000 cases of encephalitis and an estimated 500 deaths. The vaccination program has virtually eliminated the disease in this country. In 2000 the disease was declared to no longer be endemic in the U.S., meaning that the virus no longer spread on its own and the only recognized cases now come from importation from outside countries. In 2005 there was a reported low of 25 cases nationwide.

Japan, where concerns over vaccine safety have trumped immunization efforts, tells a different story. As noted in the previous MMR discussion, Japan removed the MMR vaccine in 1993; they halted mandatory immunizations altogether in 1994. Measles proliferated in that country afterwards, with an estimated 200,000 cases and 88 deaths in 2000. Finally, due to the soaring morbidity and mortality from measles, Japan returned to a routine two-dose vaccine schedule in 2006, aiming to eliminate measles from the country.

Measles has likewise started to return to countries across Europe as more people are opting-out or delaying immunization of their children due to spreading vaccine phobia in the past decade. Many people make this decision based upon the current low risk of measles in countries where vaccination rates have been high. England, once cleared of endemic measles, has declared that measles is once again an endemic disease as a direct result of decreasing immunization rates. The problem is that when immunization rates drop and enough people are unprotected, the highly contagious measles virus can quickly spread. This occurred in the late 1980s, leading to 55,000 cases, 11,000 hospitalizations and 120 deaths in the U.S. from 1989-1991. The U.S. is again witnessing a growing number of measles outbreaks and the highest case numbers seen in more than a decade, once again because of declining immunization rates. We are quite likely to follow in the European path with a return to endemic measles across this country. Our community has some special risk factors for an outbreak of measles. These include proximity to Mexico where immunization rates are lower, a major international airport bringing travelers from around the globe through our area, a sizable Asian population that frequently travels to their home countries (where measles is still prevalent) often taking their children before they are old enough to receive the measles vaccine, and an educated, affluent population that is increasingly being swayed to refuse or delay vaccination out of fears about safety. According to a study from the Journal of the American Medical Association, children exempted from vaccines by their parents had a 33 times higher rate of getting the measles during the last era of big outbreaks in the

early 1990s. When considering all of the above factors, we feel a great sense of importance in maintaining a high immunization rate and vaccinating on schedule to prevent measles from attacking our patients and our community.

One final comment comes from the founding father, Benjamin Franklin. In the 1700s, small pox was a common and very deadly infection (now eradicated from the globe by a successful program of worldwide vaccination). It was found that small pox could be prevented by inoculating children with debris from the active pox lesions of an infected person, basically causing a milder case of the disease providing protective immunity from the natural infection. This practice was risky; some children developed full blown small pox and even died, but the risk was much lower than the risk of acquiring natural infection. Ben Franklin was a vocal critic of the small pox inoculation program. Tragically, his youngest son, Franky, died from small pox infection. In his autobiography, he wrote

In 1736 I lost one of my sons, a fine boy of four years old by small pox, taken in the common way. I long regretted, and still regret, that I had not given it to him by inoculation. This I mention for the sake of parents who omit that operation that they should never forgive themselves if a child died under it.

It is our hope that we can listen to this voice of our nation's past and refuse to be manipulated by irrational fear. Our children deserve to be protected from unnecessary risks. In this vain, we encourage you to follow-up with any questions that remain about the importance and safety of each vaccine that your child will receive. We offer the following references and will gladly point you to any reference of statistics or studies mentioned in the pages above.

Vaccine Information sheets:

<http://www.cdc.gov/vaccines/Pubs/vis/default.htm>

Vaccine Preventable Disease Websites

www.cdc.gov/nip

www.aap.org

www.immunizationinfo.org

www.vaccine.chop.edu

Recommended Books:

Autism's False Prophets by Paul Offit

Deadly Choices: How the antivaccine movement threatens us all by Paul Offit

Unstrange Minds by Roy Richard Grinker

Do Vaccines Cause That?! by Martin G. Myers and Diego Pineda

Autism and Asperger Syndrome: the facts by Simon Baron-Cohen

The Panic Virus by Seth Mnookin