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The association between the measles, mumps, and rubella vaccine and the development of autism: A meta-analysis

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The Association between the Measles, Mumps, and Rubella Vaccine and the
Development of Autism: A Meta-Analysis

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
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The Association between the Measles, Mumps, and Rubella Vaccine and the Development of Autism: A Meta-Analysis

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ABSTRACT

Autism is a childhood developmental disorder characterized by impaired social interaction, difficulty with verbal and nonverbal communication and limited activities. The root cause of autism is unknown. However it has been postulated that administration of the measles, mumps, and rubella (MMR) vaccine may be causally related to the development of autism. MMR vaccination is a requirement for entry into schools, so any increase in adverse events associated with the vaccine carries widespread public health importance.

The primary objective of this study was to conduct a meta-analysis of the association between the MMR vaccination and the development of autism. The meta-analysis was limited to studies with an experimental design, unvaccinated control group, and odds ratio or relative risk as the effect measure. Both the fixed effects and random effects models were applied.

A total of 29 studies were identified for possible inclusion in the meta-analysis. After applying the inclusion/exclusion criteria seven studies were included in the meta-analysis. The pooled treatment effect was weighted based on the width of the 95% confidence interval for each of the individual studies. The pooled effect measure for the seven studies was 1.052 (95% CI: 0.973, 1.138) ($P=0.202$).

An association between the MMR vaccine and the development of autism was not found in this analysis. Public health initiatives should continue to support mandatory vaccination with MMR for entry into school and steps should be taken to eliminate any barriers to vaccination. Further epidemiological studies are needed to assess the root cause of autism.

Introduction

Autism

Autism is a developmental disorder characterized by impaired social interaction, difficulty with verbal and nonverbal communication, and limited activities and interests (NINDS 2006). Autism was first characterized in 1943 by Dr. Leo Kanner of Johns Hopkins Hospital, who termed the disease early infantile autism after studying a group of 11 children (Strock 2007). The Diagnostic and Statistical Manual of Mental Disorders (DSM –IV) classifies autism as one disease in a class of developmental disorders referred to as autism spectrum disorders (ASDs) or pervasive developmental disorders (PDDs) (Strock 2007, NINDS 2006). Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified along with autism make up the ASDs. Autism is the most common of the ASDs with an estimated three to six children out of 1,000 developing the disorder (NINDS 2006).

The most common sign of autism is impaired social interaction. Autistic children usually do not know how to play interactively with other children (NINDS 2006). Autistic children commonly have difficulty learning and understanding the normal give-and-take of social interaction. Autistic children are typically slow to learn to interpret what others are thinking or feeling. At times they may appear to be indifferent to others. This lack of social interaction results in the perception that they prefer to be alone (Strock 2007).

Other common signs include problems with verbal and nonverbal communication, repetitive behavior, and obsessive interests (NINDS 2006). In some cases autistic children remain mute their entire life. Some autistic children develop verbal skills at a much later age than their peers. Others will develop skills at a normal age but have difficulty communicating with others (Strock 2007). Additionally, autistic children often engage in repetitive behavior such as rocking or twirling (NINDS 2006). In most cases autistic children need and seek consistency in their environment. The smallest changes in daily routines can be very disturbing for autistic children.

In addition to the developmental challenges associated with autism, autistic children are at higher risk for several comorbid conditions including fragile X syndrome, tuberous sclerosis, epileptic seizures, Tourette syndrome, learning disabilities, and attention deficit disorder. Fragile X syndrome is an inherited form of mental retardation named for the part of the X chromosome that has a defective piece that appears pinched and fragile when viewed under a microscope. Tuberous sclerosis is a genetic disorder that causes benign tumors to grow in the brain and other vital organs (Strock 2007). Approximately 20 to 30% of autistic children will develop epileptic seizures by adulthood (NINDS 2006). In most cases the seizures can be controlled with pharmacologic therapy. Most autistic children will have some degree of learning disability, with the degree of disability varying by child. Often times, some areas of ability are normal, while one or more areas will show developmental delay.

The diagnosis of autism is challenging as autism varies widely in symptoms. Symptoms can range from mild to severe. Parents are often the first to notice any symptoms of autism in their child. There are several screening tools that can assist in the

screening for autism such as the Checklist of Autism in Toddlers, the Screening Tool for Autism in Two-Year-Olds and the Social Communication Questionnaire (Strock 2007). In order to establish an accurate diagnosis of autism, a comprehensive evaluation is required (NINDS 2006). The evaluation should be performed by a multidisciplinary team consisting of a psychologist, neurologist, psychiatrist and speech therapist (NINDS 2006). Evaluation tools such as the Autism Diagnosis Interview Revised and the Autism Diagnostic Observation Schedule help in evaluating a child for autism. The Autism Diagnosis Interview Revised is a structured interview of 100 questions consisting of four major factors: communication, social interaction, repetitive behaviors, and age of onset. The Autism Diagnostic Observation Schedule is an observational measure used to detect behaviors that are absent, delayed, or abnormal in children (Strock 2007).

The National Institute of Neurological Disorders and Stroke list the following core behaviors that doctors rely on for a diagnosis of autism:

- Impaired ability to make friends with peers
- Impaired ability to initiate or sustain a conversation with others
- Absence or impairment of imaginative and social play
- Stereotyped, repetitive, or unusual use of language
- Restricted patterns of interest that are abnormal in intensity or focus
- Preoccupation with certain objects or subjects
- Inflexible adherence to specific routine or rituals

The diagnosis of autism is often complicated by other autism spectrum disorders. Children with insufficient symptoms to meet the criteria for autism are often classified as having pervasive developmental disorder not otherwise specified. Children with

Asperger syndrome present with autistic symptoms but have well developed language skills (NINDS 2006). Tools such as the Autism Spectrum Screening Questionnaire, the Australian Scale for Asperger's Syndrome, and the Childhood Asperger Syndrome Test can help to distinguish Asperger syndrome from autism (Strock 2007). Children with childhood disintegrative disorder develop normally and then deteriorate between the ages of 3 to 10, showing significant autistic symptoms (NINDS 2006). After a diagnosis of autism is made, the next step is to identify appropriate treatment for the autistic child.

Currently there is no cure for autism and there is no single best treatment regimen for all children. Current therapy is designed to alleviate specific symptoms and improve functional ability. Treatment falls into two broad categories: educational/behavioral interventions and pharmacologic therapy. Educational interventions include skill-oriented sessions to help children develop social and language skills along with family counseling for parents and siblings of autistic children. Pharmacologic therapy includes antidepressants to treat depression, anxiety, or obsessive compulsive disorder or anti-psychotics to treat severe behavioral symptoms (NINDS 2006).

The selective serotonin reuptake inhibitors such as fluoxetine, sertraline, and fluvoxamine are commonly used off-label to treat depression, anxiety, and obsessive compulsive disorder in autistic children. In 2004, the Food and Drug Administration issued a "black box warning" alerting the public of the increased risk of suicidal ideation or suicide attempts in children and adolescents taking antidepressants. In October 2006, the Food and Drug Administration approved risperidone for the symptomatic treatment of irritability in autistic children, representing the first drug with an FDA approved indication to treat symptoms in autism (Strock 2007). In cases where autistic children

experience seizures, anticonvulsants are indicated. Commonly prescribed anticonvulsants include: carbamazepine, lamotrigine, topiramate, and valproic acid. Autistic children with attention deficit disorder or hyperactivity can be treated with stimulant drugs, such as methylphenidate (Strock 2007). There are also several controversial therapies available, but few if any have been scientifically proven to be effective (NINDS 2006).

The root cause of autism is unknown to date, and as of yet a biological marker for autism has not been found. Several causative factors have been offered including genetics, environmental factors, abnormal levels of serotonin or other neurotransmitters in the brain, and vaccine administration. It is strongly suspected that genetics plays some role because families with one autistic child have an approximately 5 percent risk of autism in a second child, which is much higher than the risk in the general population (NINDS 2006). MRI studies of the brain have shown that many areas of the brain are abnormal in autism including the cerebellum, cerebral cortex, limbic system, corpus callosum, basal ganglia, and brain stem. Research is ongoing to study what role these areas of the brain have in the development of autism along with the possible role of neurotransmitters such as serotonin, dopamine, and epinephrine (Strock 2007).

In the past few years there has been widespread public concern regarding a proposed theory that autism was linked to vaccine administration. The proposed link between autism and vaccines was first reported by Wakefield and colleagues in a case series study of 12 children with chronic enterocolitis and regressive developmental disorder (Wakefield 1998). In 8 of the 12 children, the onset of behavioral problems was retrospectively linked to the measles, mumps, rubella (MMR) vaccination by a parent or

physician. The Wakefield study gave rise to the proposed association of the MMR vaccine and the development of autism and created a major debate on the safety of the MMR vaccination. Since the publication of the Wakefield study, several other studies have been conducted assessing the association between MMR vaccination and the development of autism. Due to a lack of randomized controlled trials and conflicting results, there has not been enough evidence to support or definitively refute the hypothesized association between MMR and autism.

Measles, Mumps, Rubella

Measles

Since the inception of vaccinations for measles, mumps, and rubella the number of cases of these diseases has decreased by 99%. The success of the vaccinations has led to an attempt to eliminate these diseases. A goal of the 1993 Childhood Immunization Initiative was to eliminate indigenous transmission of measles and rubella in the United States by 1996 (CDC 1998). While these goals have not yet been achieved it appears that vaccination makes these goals feasible in the near future.

The first of these three diseases- measles also referred to as rubeola- is a disease characterized by a total body skin rash. Measles is a highly contagious disease with an incubation period of 10-12 days from exposure to prodrome and 14 days from exposure to rash. In the United States 1-2 out of every 1,000 cases results in death. Infants and young children are at higher risk of death from measles and its complications. The most severe complications of measles infection are pneumonia and acute encephalitis. The rate of death from measles in less developed countries can be as high as 25%. In 1963

the first measles vaccine was licensed. Prior to this time an average of 400,000 measles cases were reported each year in the United States. Since the inception of the measles vaccine, the number of cases of measles has decreased by 99% (CDC 1998). Measles experienced a resurgence in the United States from 1989 to 1991. There were more than 55,000 cases of measles and over 120 measles related deaths. The resurgence was led to a large degree by a number of unvaccinated preschool aged children residing in urban areas.

In 1989 the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommended that all children receive two doses of a measles-containing vaccine. The implementation of the vaccination policy led to a decrease in the number of measles cases from 2,237 cases in 1992 to only 312 cases in 1993. The challenges to eliminating and sustaining the elimination of measles are: 1) continuing to vaccinate all children aged 12-15 months with a first dose of MMR, 2) ensuring that all children have received a second dose of MMR before entering school, and 3) working with other countries to achieve measles elimination goals (CDC 1998).

Mumps

Mumps is a disease characterized by bilateral or unilateral parotitis. The average onset of mumps is 16-18 days after exposure with nonspecific symptoms such as fever, headache, malaise, myalgia, and anorexia preceding parotitis. Approximately 15%-20% of all mumps cases are asymptomatic and up to 50% of cases are associated with nonspecific respiratory symptoms. The most serious complications of mumps such as male sterility and aseptic meningitis are more likely to occur in adults than children (CDC 1998).

The mumps vaccine was first licensed in the United States in 1967. Since the inception of the mumps vaccine, reported cases of mumps have decreased by 99% from 185,691 cases in 1968 to only 906 cases in 1995. State laws requiring that children be vaccinated before school entry have significantly contributed to the decrease in reported cases of mumps. The current two dose schedule of MMR likely further decreases the mumps incidence by immunizing children with a second dose as not all children generate an immune response following the first dose (CDC 1998).

Rubella

Rubella is a disease characterized by nonspecific signs and symptoms including a pruritic rash, arthralgia, and low-grade fever. The average incubation period is 12 to 23 days and between 25-50% of all cases are subclinical. Congenital rubella syndrome carries the risk of severe consequences such as miscarriages, stillbirth, fetal anomalies, and therapeutic abortions. Children born with congenital rubella syndrome often have several abnormalities including sensory deficits, ophthalmic deficits, mental retardation, microcephaly, pulmonary artery stenosis, and atrial or ventricular septal defects (CDC 1998).

During the last major outbreak of rubella in the United States from 1964-1965, there were an estimated 20,000 cases of congenital rubella syndrome from 1964-1965. This led to the first rubella vaccine being licensed in 1969 with a target of children in kindergarten and the early grades of elementary school. Following the initial vaccination campaign, cases of congenital rubella decreased by 69% from 1970 to 1976. However, rubella outbreaks continued to occur in older adolescents and young adults. ACIP modified the recommendations for immunization to include the vaccination of post

pubertal girls and women in 1977. Cases of congenital rubella syndrome and rubella have occurred at a relatively constant endemic level with an average of less than 200 cases with an occasional outbreak in persons over the age of 20 years. An accurate incidence rate for rubella is difficult to estimate because rubella surveillance in the United States relies on a passive system (CDC 1998).

Vaccine Preparations

Measles, mumps and rubella (MMR) vaccines are available as a combination vaccine, as well as monovalent vaccine for each specific agent. Vaccines are also available as a combination of measles-rubella and a combination of rubella-mumps. Excipients included in each dose of the combined or monovalent vaccines are 0.3 mg of human albumin, 25 µg of neomycin, 14.5 mg of sorbitol and 14.5 mg of hydrolyzed gelatin. The measles and mumps components are live vaccines produced in chick embryo cell culture and the live rubella vaccine is grown in human diploid cell culture (CDC 1998).

The strain of measles used in the vaccine has changed several times since the vaccine was first licensed in 1963. Originally, both a live and an attenuated strain of vaccine were available. Currently, only the Enders-Edmonston strain of measles licensed in 1968 is available in the United States. Upon vaccination the measles vaccine produces a mild, noncommunicable infection with antibodies developing in 95% of children vaccinated at 12 months and 98% of children vaccinated at age 15 months. Serologic and epidemiologic evidence indicates that the vaccine produces lifelong immunity in most persons (CDC 1998)

The strain of rubella used in vaccines is a live strain of RA 27/3 first licensed in 1979. Serologic immunity is achieved in 95% of people aged 12 months or older who receive at least one dose of rubella vaccine. Greater than 90% of vaccinated individuals have protection against both clinical rubella and viremia for at least 15 years. There have been several reports of viremic reinfection following exposure among vaccinated individuals with low levels of detectable antibodies. Additionally, rare cases of congenital rubella syndrome have occurred in infants born to mothers with documented serologic evidence of rubella immunity before they became pregnant (CDC 1998).

The mumps vaccine contains the live Jeryl-Lynn strain of mumps. Vaccination with mumps vaccine produces a subclinical infection with few side effects. In controlled clinical trials, over 97% of those vaccinated develop measurable immunity following vaccination. Studies in the field report that the efficacy of the vaccine ranges from 75% to 95%. Serologic and epidemiologic evidence suggest continuing protection against infection although the duration of immunity is unknown (CDC 1998).

Vaccine Administration

The Advisory Committee on Immunization Practices (ACIP) recommends the combined MMR vaccine as the vaccine of choice to protect against all three diseases unless contraindicated. Two doses should be administered separated by at least one month in all children on or after their first birthday and in high risk adolescents and adults. The second dose of MMR should elicit a response in the few individuals who do not elicit an immunological response to at least one component following their first vaccination. Administering the vaccines in combination produces a similar response to receiving single-antigen vaccinations with measles, mumps, and rubella vaccines at

different sites or different times. ACIP supports the administration of the MMR vaccine at the same time as other vaccines such as diphtheria, tetanus toxoid and acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), oral polio vaccine or inactivated polio vaccine according to the schedule to receive vaccines (CDC 1998). (See Appendix A)

ACIP recommends that all children receive their first dose of MMR vaccine at age 12-15 months. In certain high risk areas it is recommended that children receive their first dose by 12 months. High risk areas are defined as:

- A county with a large inner city population,
- A county where a recent measles outbreak has occurred among unvaccinated preschool-aged children, or
- A county in which more than five case of measles has occurred among preschool-aged children each of the last 5 years.

ACIP recommends that the second dose of MMR vaccine be administered when children are aged 4-6 years. ACIP, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) have jointly adopted the recommended timing of the second dose of MMR. ACIP encourages all states to adopt the two dose MMR requirement for preschool-aged children so that all 50 states will have a universal policy requiring:

- For preschool-aged children: documentation of at least one dose of MMR vaccine administered on or after the first birthday, and

- For children in kindergarten through grade 12: documentation of two doses of MMR vaccine separated by at least 28 days with the first dose administered no earlier than the first birthday (CDC 1998).

ACIP recommends that all people born in 1957 or later who do not have a contraindication to the MMR vaccine should receive at least one dose. People born before 1957 are considered to be immune to measles, mumps, and rubella. People considered being at high risk such as international travelers, persons attending colleges, and persons who work at healthcare facilities should receive special consideration for vaccination. Additionally, all women of childbearing age who do not have acceptable evidence of rubella immunity should be offered vaccinations whenever they contact the healthcare system (CDC 1998).

MMR Adverse Events

The range of adverse effects following the administration of the MMR vaccine ranges from common adverse events such as local pain and edema to the rare case of anaphylaxis. An expert committee at the Institute of Medicine determined that evidence supports a causal relationship between MMR vaccination and anaphylaxis, thrombocytopenia, febrile seizures, and acute arthritis (CDC 1998). Other adverse events reported in the MMR package insert include: vasculitis, otitis media, conjunctivitis, optic neuritis, ocular palsies, Guillan-Barre syndrome and ataxia (M-M-R II 2007).

In response to the adverse events caused by all vaccines including the MMR vaccine, The National Vaccine Injury Compensation Program (VICP) was created by the National Childhood Vaccine Injury Act of 1986. VICP works to resolve vaccine injury claims by providing compensation for people found to be injured by certain vaccines.

The US Department of Health and Human Services, the US Department of Justice, and the US Court of Federal Claims all have a role in VICP. Compensation for injured parties as a result of vaccine administration is determined by the US Court of Federal Claims (HRSA). VICP covers the following vaccines:

- Diphtheria, tetanus, pertussis (DTaP)
- *Haemophilus influenzae* type b
- Hepatitis A and Hepatitis B
- Human Papillomavirus
- Influenza
- Measles, mumps, rubella (MMR)
- Meningococcal
- Polio
- Pneumococcal conjugate
- Rotavirus
- Varicella

Any person who has received a vaccine covered by VICP that believes that they were injured as a result of that vaccine may file a claim. To file a claim the effects of the injury must have: 1) lasted for more than 6 months after the vaccine was given; or 2) resulted in a hospital stay and surgery; or 3) resulted in death. There is no limit on the amount of compensation an injured party may receive. The amount compensated is determined as a reasonable amount for past and future medical and custodial care costs and related expenses, lost earnings, reasonable lawyer fees and up to \$250,000 for actual and projected pain and suffering. A claim must be filled within 3 years after the first

symptom of the vaccine related injury or within 2 years of death or 4 years after the first symptom of the vaccine related injury (HRSA 2008).

Since the inception of VICP there have been 774 claims against the MMR vaccine. A total of 271 cases resulted in compensation being paid to the claimant, 323 claims were dismissed, and 180 claims are still pending. Since 1989, there have been 2,865 claims filed for non-autism related injuries and 5,263 claims for autism related injuries across all vaccinations. Since 1990, only one autism case has been deemed compensable to date and 350 cases have been dismissed (HRSA 2008). The remaining autism-related cases are still awaiting a ruling. The debate of whether autism is causally linked to vaccine administration and therefore should be compensated under VICP is still ongoing and has a potentially significant impact on public health.

Table 1. National Vaccine Injury Compensation Program-Post 1988 Statistics Report of Petitions Filed

Fiscal Year	Non-Autism	Autism	Total
FY 1989	1	0	1
FY 1990	29	0	29
FY 1991	118	0	118
FY 1992	186	0	186
FY 1993	137	0	137
FY 1994	106	0	106
FY 1995	179	0	179
FY 1996	84	0	84
FY 1997	103	0	103
FY 1998	116	0	116
FY 1999	405	1	406
FY 2000	161	0	161
FY 2001	196	18	214
FY 2002	189	768	957
FY 2003	152	2,437	2,589
FY 2004	126	1,088	1,214
FY 2005	146	587	733
FY 2006	154	169	323
FY 2007	238	168	406
FY 2008	39	27	66
Total	2,865	5,263	8,128

Table 2. National Vaccine Injury Compensation Program Post 1988 Statistics Report for Adjudications of Claims

Fiscal Year	Non-Autism			Autism			Total
	Compensable	Dismissed	Sub-Total	Compensable	Dismissed	Sub-Total	
FY 1990	2	0	2	0	0	0	2
FY 1991	10	22	32	0	0	0	32
FY 1992	30	43	73	0	0	0	73
FY 1993	22	57	79	0	0	0	79
FY 1994	41	43	84	0	0	0	84
FY 1995	48	51	99	0	0	0	99
FY 1996	50	78	128	0	0	0	128
FY 1997	60	51	111	0	0	0	111
FY 1998	53	72	125	0	0	0	125
FY 1999	38	73	111	0	0	0	111
FY 2000	67	75	142	0	0	0	143
FY 2001	66	79	145	0	0	0	145
FY 2002	98	95	193	0	4	4	197
FY 2003	52	74	126	0	21	21	148
FY 2004	60	120	180	0	113	113	293
FY 2005	60	69	130	0	51	51	181
FY 2006	67	76	145	0	107	107	249
FY 2007	80	71	151	0	32	32	183
FY 2008	21	9	30	1	22	23	53
Totals	924	1,158	2,082	1	350	351	2,433

Thimerosal

A second hypothesis dealing with vaccine administration and the development of autism contends that thimerosal, a mercury containing preservative that has been used in some vaccines and other pharmaceutical products since the 1930s, is the agent causing autism. Thimerosal was contained in over 30 childhood vaccines including *Haemophilus influenzae* type b, hepatitis B, and DTaP up until 1999. Thimerosal was never used as a preservative for the MMR vaccine because thimerosal would inactivate the live vaccine. The thimerosal hypothesis gained credibility after FDA researchers determined that the

childhood vaccination schedule might expose children to cumulative doses of ethyl-mercury that exceed some federal safety guidelines (IRSC 2004). In 2001, the Institute of Medicine concluded that the evidence was inadequate to accept or reject a causal relationship between exposure to thimerosal and the development of autism (IRSC 2004). As of March 2001, all formulations of vaccines for childhood immunizations are free of thimerosal (IRSC 2004).

Healthy People 2010

Healthy People 2010 is a declaration of the national health objectives designed to identify the most significant preventable threats to health and to establish national goals to reduce these threats. The two primary goals of Healthy People 2010 are to increase the quality and duration of healthy life and to eliminate health disparities. There are 28 focus area chapters in Healthy People 2010 and each chapter contains a concise goal statement. The goal of Healthy People 2010 pertaining to immunizations and infectious disease is to prevent disease, disability, and death from infectious diseases, including vaccine preventable diseases (Healthy People 2010).

Healthy People 2010 includes specific goals and objectives under each chapter outlining goals and methods for improving health. The overall goal of Chapter 14: Immunization and Infectious Diseases, is to reduce or eliminate indigenous cases of vaccine-preventable diseases. Healthy People 2010 attempts to build upon the progress that was made toward meeting the Healthy People 2000 objectives. As an example, the number of cases of measles decreased from 3,396 indigenous cases in 1988 to only 74

cases in 1998 (Healthy People 2010). A primary objective under this goal is the elimination of all cases of measles, mumps, and rubella.

The achievement of a high level of coverage for two doses of MMR vaccine makes the goal of eliminating measles, mumps, and rubella feasible. In 1998 the baseline immunization rate for at least one dose of the MMR vaccine was 92%. The Healthy People 2010 goal is to maintain at least 90% coverage for one dose of the MMR vaccine. It is believed that coverage of at least 90% is sufficient to prevent the circulation of viruses and bacteria-causing disease. However, even with the achievement of 90% coverage levels it is imperative to monitor subgroups of the population that are under vaccinated. These groups of under vaccinated individuals increase the possibility of a major outbreak of a vaccine preventable disease. Eliminating potential health disparities is a necessary measure to achieving the goal of eliminating all cases of measles, mumps, and rubella (Healthy People 2010).

Another objective of the chapter on immunization and infectious diseases from Healthy People 2010 that builds upon Healthy People 2000 is to maintain vaccination coverage levels for children in licensed day care facilities and children in kindergarten through the first grade. The goal for the MMR vaccine is 95% for children in day cares and children in kindergarten to first grade. As measured in Healthy People 2000, the individual coverage rates for three or more doses of polio, three or more doses of diphtheria/tetanus/acellular pertussis (DTaP), one or more doses of MMR and three or more doses of *Haemophilus influenzae* type b vaccines were each at or above 91 percent (Healthy People 2010). Increasing the coverage rate to 95% for all children entering a

licensed day care facility or entering school represents a significant step to eliminating all cases of vaccine preventable diseases.

Healthy People 2010 also outlines strategies to achieve the outlined goals and objectives. Major strategies to protect people from vaccine preventable diseases include:

- Improving the quality and quantity of vaccination delivery services,
- Minimizing financial burdens for needy persons,
- Increasing community participation, education and partnership,
- Improving monitoring of disease and vaccination coverage rates, and
- Developing new or improved vaccines and improving vaccine use.

Programs such as Vaccines for Children and SCHIP have made vaccinations available for children. These programs along with the requirements of vaccinations for entry into day care and schools have increased the vaccination rate (Healthy People 2010).

Improvements in the vaccination rate not only extend benefits to those that are vaccinated, benefits of vaccination are gained by society as a whole. In cases where a few people cannot be vaccinated, if the vaccination level in the community is high these people are protected due to group or “herd” immunity, whereby the unvaccinated group has a decreased risk of contracting a disease because all those around them have been vaccinated. Achievement of the Healthy People 2010 MMR vaccination goals will go a long way toward eradicating measles, mumps, and rubella.

It is hypothesized that administration of the MMR vaccine is causally related to the development of autism. The hypothesis was first proposed by Wakefield and associates (Wakefield1998) following a case study of 12 children with gastrointestinal disorders and developmental regression. In 8 of the 12 children, the parents or the

physician retrospectively linked the onset of the behavioral problems with the administration of the MMR vaccine. While the authors concluded that there was insufficient evidence in their study to support a causal relationship, the study generated a hypothesis warranting further research. The purpose of this research is to evaluate if a causal relationship exists between childhood vaccination with MMR and the development of autism by applying the statistical methods of a meta-analysis of published primary literature.

Methods

The primary objectives of this analysis are to:

1. Assess the causal relationship between the MMR vaccine and the development of childhood autism, and
2. Discuss the impact of the association of the MMR vaccine and the development of autism on the ACIP vaccination guidelines and the Healthy People 2010 goal for immunizations against preventable diseases.

A quantitative meta-analysis was conducted to assess the causal relationship between the MMR vaccine and the development of autism. A comprehensive literature search of PubMed and Medline assessing the relationship between the MMR vaccine and the development of autism during the years 1998 to 2007 was conducted. Key search terms for the systematic literature review included: autism, autistic, MMR, measles, mumps, and rubella alone or in combination. The search was limited to articles published in the English language. A total of 29 studies were identified.

The following study inclusion criteria were employed on the 29 studies.

1. Appropriate study design (e.g. prospective or retrospective case-control or cohort study)
2. Study must contain a control group
3. Study endpoints must report or allow for the calculation of the effect measure and a standard error or confidence interval for the association of MMR vaccination and the development of autism (odds ratio or relative risk)

4. Experimental group must have received MMR vaccination
5. Adequate sample size ($n \geq 100$)

The following study exclusion criteria were employed:

1. Study does not have an unvaccinated comparison group (e.g. case report/case series)
2. Study endpoints do not allow for the calculation of an odds ratio or relative risk
3. Study exposure does not include the MMR vaccination
4. Study is not independent of another study included in the analysis (e.g. re-analysis of the same study population)

After applying the inclusion/exclusion criteria seven studies remained for inclusion in the meta-analysis (see Appendix B). Statistical analyses combining and interpreting the results of independent studies were conducted to integrate the results of several studies and arrive at a conclusion on the causal association of the MMR vaccine and autism.

The patient population included children (<18 years) who have received the MMR vaccine under a normal vaccination schedule according to ACIP guidelines or appropriate guidelines for their country.

Study Endpoints will include:

- Effect measure
 - Odds ratio/relative risk for each individual study
 - Pooled effect for the association between MMR vaccination and the development of autism
- Meta-regression

- Meta-regression to assess the impact of continuous predictors (e.g. age at vaccination, number of vaccinations)

The odds ratio of the association between the MMR vaccine and the development of autism was measured for each individual study as the effect measure. The pooled effect measure was then calculated based on the weighted average of the effect measures seen in each study. The weight for each study was determined based on the width of the 95% confidence interval for the effect measure of each study. The meta-analysis was conducted using both a fixed and a random effects model. A sensitivity analysis was conducted to assess the impact of individual studies on the pooled effect measure. Publication bias was assessed using a funnel plot and the trim and fill technique. Data analysis will be conducted using Comprehensive Meta Analysis (CMA) Version 2.0, a computer program for meta analysis developed by a team of experts from the US and U.K. and funded by the US National Institutes of Health.

Results

Descriptive Statistics

Seven out of 29 studies met all inclusion/exclusion criteria. Fifteen studies were excluded due to the lack of an unvaccinated control group (Studies 1, 2, 3, 5, 6, 9, 12, 13, 15, 16, 17, 21, 22, 27, and 28). Three studies were excluded for the lack of MMR exposure in the study (Studies 7, 11, and 25). Three studies were excluded because they did not allow for the calculation of an effect size (Studies 18, 19, and 29). One study was excluded because it was a secondary analysis of a previous study that was included in the meta-analysis (Study 4).

The following seven studies were included in the meta-analysis: Madsen 2002, Honda 2005, Smeeth 2004, Taylor 1999, Uchiyama 2007, Goldman 2004 and Taylor 2002.

Table 3. Synopsis of Included Studies

Study	Design	Country	Years	Dependent Variable
Madsen 2002	Retrospective cohort study	Denmark	1991-1998	Autism or ASD
Honda 2005	Cohort study	Japan	1988-1996	ASD
Smeeth 2004	Case-control study	United Kingdom	1987-2001	Autism or ASD
Taylor 1999	Epidemiological study	United Kingdom	1979-1992	Autism
Uchiyama 2007	Epidemiological study	Japan	1976-1999	ASD
Goldman 2004	Retrospective cohort study	Denmark	1980-1992	Autism
Taylor 2002	Population study	United Kingdom	1979-1992	Autism

Madsen 2002 was a retrospective cohort study of all children born in Denmark including a total of 537,303 children. Vaccination status was obtained from the National Board of Health and information on autism status was obtained from the Danish Psychiatric Central Register. A total of 316 children were diagnosed with autism and 422 with an autism spectrum disorder. The relative risk for autistic disorder in the unvaccinated group compared to the vaccinated group was 0.919.

Honda 2005 was a cohort study of children up to age seven born between 1988 and 1996 in Kohoku Ward of Japan. All children born in 1993 or after did not receive a single vaccination of MMR. The cumulative incidence of autism spectrum disorders increased significantly in the birth cohorts from 1988 through 1996 with the most notable increase beginning with the 1993 birth cohort. The odds ratio for the association between MMR and autism was 1.921.

Smeeth 2004 was a matched case-control study using the U.K. General Practice Research Database. Cases were people born in 1973 or later who were diagnosed with a pervasive developmental disorder, between 1987 and 2001. Controls were matched on age, sex, and general practice. A total of 1294 cases and 4469 controls were included in the study. The odds ratio for the association of MMR and autism was 0.880.

Taylor 1999 was an epidemiological study of children from eight North Thames health districts in the U.K. Information from clinical records of the children was linked to immunization data held on the child health computing system. Any clustering of onset of autism in post vaccination periods were investigated using the case series method. A

total of 498 cases of autism were identified. The odds ratio for the association of MMR and the development of autism was 0.940.

Uchiyama 2007 was an epidemiological study of the association between MMR vaccination and the development of autism in Japan. Since the MMR vaccine was only used in Japan between 1989 and 1993, this time period affords a natural experiment for MMR and autism. The study included an analysis on 904 patients with autism spectrum disorder. The analysis included cohorts from three periods: before, during, and after MMR usage. There were no significant differences in the incidence of autism in the cohort that received MMR and those who had not with an odds ratio of 0.744.

Goldman 2004 investigated the prevalence of autism by age category from 1980 to 2002 using a nationwide computerized registration system with the Danish Psychiatric Central Register. The MMR vaccine was added to the immunization schedule of Denmark in 1987. Linear regression analysis was used to investigate compare the periods preceding and following the introduction of the MMR vaccine. Longitudinal trends in the prevalence data suggest a temporal association between the introduction of MMR vaccine and the rise in autism with an odds ratio of 4.700.

Taylor 2002 was a population study with case note review of five health districts in north east London. The study population included 278 children with core autism and 195 with atypical autism identified from computerized disability registers born between 1979 and 1998. The odds ratio for the association of MMR and the development of autism was 0.980.

Meta-Analysis Results

Two of the seven studies included in the meta-analysis suggested a causal association between MMR and autism and five studies did not suggest a causal association. The combined effect measure using a fixed effects model was 1.052 (95% CI: 0.973, 1.138; p value= 0.202). The weights assigned for the studies based on the size of the confidence intervals under a fixed model were: 6.99% for Madsen 2002, 5.22% for Honda 2005, 8.35% for Smeeth 2004, 3.04% for Taylor 1999, 1.13% for Uchiyama 2007, 3.43% for Goldman 2004, and 71.84% for Taylor 2002. When using a random effects model, the combined effect measure was 1.267 (95% CI: 0.879, 1.827; p value=0.204). In the random effects model the studies weights were: 15.31% for Madsen 2002, 14.81% for Honda 2005, 15.56% for Smeeth 2004, 13.55% for Taylor 1999, 10.08% for Uchiyama 2007, 13.87% for Goldman 2004, and 16.82% for Taylor 2002.

Figure 1. Meta-analysis results: Autism and MMR

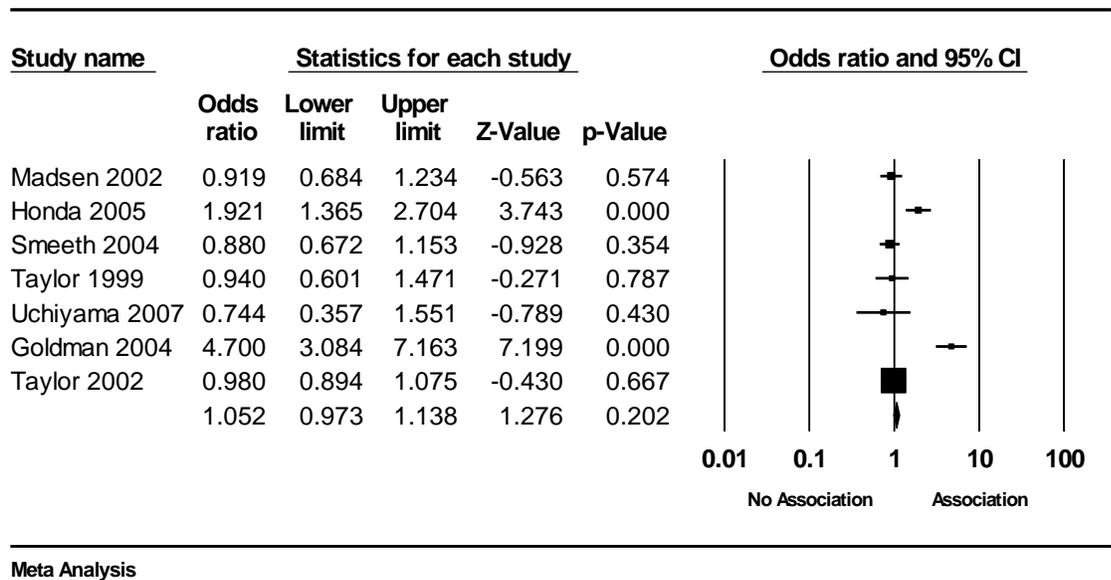
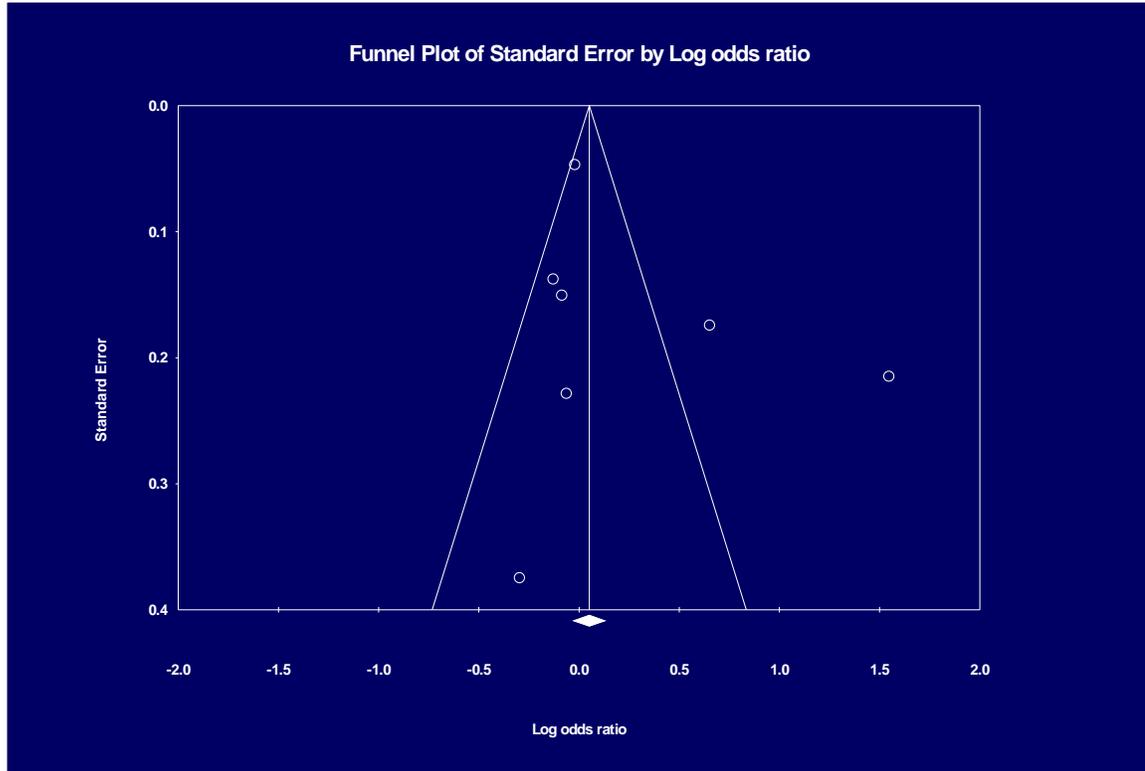


Figure 2. Meta-analysis results: Funnel Plot



Sensitivity Analysis

The meta-analysis was conducted removing the outlier study, Goldman 2004, in the sensitivity analysis. The combined effect measure for the 6 studies excluding Goldman 2004 was 0.998 (95% CI: 0.921, 1.080; p value=0.953) when using a fixed effects model. When using a random effects model the combined effect measure was 1.035 (95% CI: 0.835, 1.281; p value=0.755). The funnel plot assessing publication bias revealed no publication bias as the studies were symmetrical. Most studies assessing the association between MMR and the development of autism fall in the range of no association. The Goldman 2004 and Honda 2005 studies fall outside of the funnel, indicating that they were outliers.

Discussion

The results of this meta-analysis did not find a causal association between MMR vaccination and the development of autism. The combined fixed effect measure of 1.052 includes a 95% CI from 0.973 to 1.138 that crosses one, thus making the results non-significant. The same scenario occurs when using a random effects model with an effect measure of 1.267 and a 95% CI from 0.879 to 1.827. In both a fixed and random effects model the meta-analysis did not find a causal association between MMR vaccination and the development of autism. Due to the small number of studies included the study may not have had adequate power to detect a difference if one existed.

The two studies included in the meta-analysis that supported an association between MMR vaccination and the development of autism are potentially biased by time. Goldman 2004 examines the prevalence of autism by age category from 1980 to 2002 using a computerized registration system in Denmark. The study provided a comparison of prevalence rates pre and post licensure of the MMR vaccine. Prevalence rates in the post licensure period may have been much higher than in the pre licensure period due to greater diagnostic awareness and an overall increasing prevalence of autism.

Studies such as Dales 2001 and Kaye 2001 have found an increasing prevalence of autism over time. Dales 2001 was a time trend analysis of the association of autism and MMR vaccination coverage in California. Dales 2001 showed a sustained increase in autism cases from 44 cases per 100,000 births in 1980 to 208 cases per 100,000 live births in 1994 with minimal change in MMR vaccination rates. The changes in the

prevalence rates seen in this study provide evidence that MMR vaccination was not the cause of the increased prevalence of autism. Similarly, Kaye 2001 was a time trend analysis of autism prevalence in the UK from 1988 to 1999. The incidence of autism increased sevenfold from 1988 to 1999 with the vaccination rate staying above 95% over the entire timeframe. This suggests that some other factor was the root cause of the increasing prevalence of autism and not MMR vaccination.

The association found in Honda 2005 may have been influenced by the same time factor bias as Goldman 2004. In Honda 2005, the cumulative incidence of autism spectrum disorders were examined from 1988 to 1996 in the Kohoku ward of Japan. The population was divided into vaccinated and unvaccinated populations based on MMR vaccination being discontinued in 1993. The association that was found may have been influenced by time with the two cohorts being determined by the time when MMR vaccination was available.

There are several possible explanations for the apparent increase in autism prevalence. Changes in the prevalence of autism may be influenced by: substantial migration of affected children into or out of a community, change in age of onset or recognition, large changes in denominator population, increased ascertainment of children with diagnoses of autism, a change in diagnostic criteria to include individuals with milder symptoms, and a true increase in the incidence of the disease, which can be attributable to new environmental exposures (Halsey 2001). Studies to determine the prevalence of autism are very susceptible to bias and therefore prevalence rates in the literature vary considerably. The increased attention and better understanding of autism

has likely led to a greater diagnostic awareness accounting for a portion of the increased prevalence.

Vaccination rates and vaccine safety are major issues of concern for public health. An adequate vaccination history is routinely a requirement for school entry. Reasonable concerns about the safety of childhood vaccines would require an examination of the vaccine schedule and the legality of requiring children to be vaccinated before entering school. The evidence in this case did not find a causal association between MMR vaccination and the development of autism. As such, public health initiatives should focus on achieving the Healthy People 2010 goals of eliminating vaccine preventable diseases. Measles, mumps, and rubella pose significant risks to the health of unvaccinated children. Media attention and parental concern about the safety of the MMR vaccine has led some parents to withhold the vaccination from their child. Disseminating evidence on the safety of the MMR vaccine should be a major public health initiative. Educating parents on the safety of the vaccine and the potential dangers of measles, mumps, and rubella is the first step to increasing the vaccination rate and eventually eliminating these three diseases.

In order to adequately address the problem of autism more information is needed on the root cause of the disease. Areas that require further study include factors associated with autism including genetics and environmental exposure in utero and during the first few months after birth, or temporally associated with the onset of symptoms (Halsey 2001). One of the primary reasons that MMR vaccination was believed to be a cause of autism was the close temporal relationship between MMR vaccination and the onset of symptoms. According to the Recommended Vaccination

Schedule (Table 1), the MMR vaccine is given at 12-15 months, which coincides with the typical onset of autism. During the 12-15 months of age period, children are receiving several vaccines that may have some role in the development of autism. Additionally, presentation with autism at this early age would suggest that there may be genetic or in utero factors that are causally associated with autism development. Weiss and associates reported an association between microdeletion and microduplication on chromosome 16p11.2 (Weiss 2008). This novel microdeletion and microduplication carries a substantial susceptibility to autism, but it only accounts for approximately 1% of all autism cases. The identification of this one genetic factor responsible for 1% of all autism cases may be just the beginning of uncovering the genetic link to autism.

Another area for future research is the incidence of regression in people with autism. Wakefield and associates first hypothesized that the MMR vaccine was associated with a 'regressive' phenotype of autism (Wakefield 1998). Further study on the nature and incidence of people with 'regressive' autism may show a certain group of individuals who are genetically predisposed or have some other factor that triggers regressive autism. It may be possible that the MMR vaccine or some other environmental exposure around the time of MMR vaccination may trigger the onset of regressive autism.

There is the potential that a previously unrecognized infectious agent may affect persons with autism. A close temporal relationship between MMR vaccination and onset of autism symptoms led to the proposed causal association. In the 12-15 months of life before MMR vaccination, children are exposed to several potentially infectious agents. Like previous infectious diseases such as HIV, it may be years before a causative

pathogen is identified. It is vital that continued scientific efforts be directed to the identification of the cause or causes of autism and ways to avoid this debilitating disease.

The strengths of this study include population-based data, inclusion of an unvaccinated control group, and large total sample size. Limitations of the study include small number of studies included, retrospective data collection for some studies, differences in the dependent variable, differences in vaccination policies across countries, recording of data may have been incomplete or inaccurate, and the inability to control for potential confounders such as time, greater diagnostic awareness and age at vaccination. The quality of the meta-analysis is limited by the limitations of each individual study.

Conclusion

This study does not support a causal association between the MMR vaccine and the development of autism. Public health initiatives are needed to promote the safety of the MMR vaccine and to increase the vaccination rate. Increasing the vaccination rate for MMR will generate progress toward eliminating measles, mumps, and rubella as childhood diseases. Further epidemiological research on the root cause of autism should focus on a genetic link or environmental factors in the early stages of life.

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Appendices

Appendix A Recommended Immunization Schedule

Table 4. Recommended Immunization Schedule for Ages 0-6

Vaccine	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years
Hepatitis B	Hep B	Hep B			Hep B						
Rotavirus			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP		DTaP				
<i>Haemophilus influenzae</i> type b			Hib	Hib	Hib	Hib					
Pneumococcal			PCV	PCV	PCV	PCV				PPV	
Inactivated Poliovirus			IPV	IPV	IPV						
Influenza					Yearly						
Measles, Mumps, Rubella						MMR					MMR
Varicella						Varicella					
Hepatitis A						HepA (2 doses)				Hep A Series	
Meningococcal										MCV4	

Key: = Range of recommend ages = Certain high-risk groups

Adapted from: Recommended Immunization Schedule for Persons Aged 0-6 Years- United States 2008. Approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics and the American Academy of Family Physicians. Available at: www.cdc.gov/vaccines/recs/schedules

Appendix B Research Review

Table 5. Research Review

Citation	Design Information	Outcome Measures	Results	Key Assumptions/ Limitations	Inclusion/ Exclusion
<p>1. Dales L, Hammer SJ, Smith NJ. Time trends in autism and MMR immunization coverage in California. <i>JAMA</i> 2001;285(9): 1183- 1185.</p>	<p>Objective: To determine if a correlation exists in secular trends of MMR immunization coverage among young children and autism occurrence</p> <p>Methods: Retrospective analysis of MMR immunization coverage rates in children in California kindergartens and of autism caseloads among children who were enrolled in the California Department of Development Services</p>	<ul style="list-style-type: none"> • MMR immunization coverage rates as of 17 months and 24 months and numbers of autism cases, grouped by year of birth 	<p>No correlation was found; sustained increase in autism cases, while changes in immunization coverage were much smaller and of shorter duration</p>	<ul style="list-style-type: none"> • Immunization at 17 months used because this is just before the mean age when parents first notice developmental disorders • Immunization and autism records on the same individuals could not be linked 	<p>Excluded - Autism and immunization records not linked to be able to determine a control group</p>

Appendix B (Continued)

<p>2. DeFastano F, Bhasin TK, Thompson WW, et al. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. <i>Pediatrics</i> 2004;113: 259-266.</p>	<p>Objective: To compare age at first MMR vaccination between children with autism and children who did not have autism</p> <p>Methods: Case-control study using vaccination data abstracted from immunization forms for school entry</p>	<ul style="list-style-type: none"> • Odds Ratio determined by conditional logistic regression 	<p>No significant associations for any age cutoff were found for specific case subgroups; More cases than control were vaccinated before 36 months (OR 1.49; OR 1.23 in the birth certificate cohort)</p>	<ul style="list-style-type: none"> • MMR vaccine increases the risk of autism, which usually develops before 24 months of age, if so then children vaccinated at younger ages would have a higher risk of developing autism • Compared cases and controls because they did not have an unvaccinated group and had incomplete information for determining the date of onset of autism 	<p>Excluded -Study did not have a control group that was unvaccinated</p>
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Appendix B (Continued)

<p>3. DeWilde S, Carey I, Richards N, et al. Do children who become autistic consult more often after MMR vaccination? <i>Br J Gen Pract.</i> 2001;51: 226-227.</p>	<p>Objective: To assess changes in parental concern as measured by a change in consultation behavior following MMR vaccination</p> <p>Methods: Case-control study using the Doctor's Independent Network database to count the number of consultations</p>	<ul style="list-style-type: none"> • Number of consultations before and after the MMR vaccination 	<p>No significant differences in the numbers of consultations in the 6 months before and two months after MMR between cases and control</p>	<ul style="list-style-type: none"> • Cases of autism could not be confirmed • Cases and controls both received the MMR vaccination 	<p>Excluded -Study does not have an unvaccinated control group</p>
<p>4. Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. <i>Vaccine</i> 2001;19: 3632-3635.</p>	<p>Objective: To test the hypothesis that MMR vaccination causes autism without pre-specifying any fixed time interval after vaccination in which the risk of autism might be increased</p> <p>Methods: Self-matched case series study</p>	<ul style="list-style-type: none"> • Relative incidence for autism diagnosis or regression following MMR vaccination 	<p>In all instances the relative incidences did not differ significantly from 1, indicating no association between vaccination and autism in the subsequent risk periods</p>	<ul style="list-style-type: none"> • Study includes data on all MMR vaccines, including those given later than the recommended schedules 	<p>Excluded -Second analysis of same study population; follow-up analysis of Taylor et al. (Lancet 1998)</p>

Appendix B (Continued)

<p>5. Fombonne E, Zakarian R, Bennett A, et al. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. <i>Pediatrics</i> 2006;118: e139-e150.</p>	<p>Objective: To estimate the pervasive developmental disorders in Montreal from 1987 to 1998 and to evaluate the relationship with changes in cumulative exposure to ethylmercury (thimerosal) and trends in MMR vaccination use rates</p> <p>Methods: Cohort study of children born between 1987 and 1996 using surveys of vaccination rates and thimerosal exposure</p>	<ul style="list-style-type: none"> • Odds Ratio for thimerosal exposure • Odds Ratio for MMR vaccination use rates 	<p>No significant effects of thimerosal exposure on the risk of developing a pervasive developmental disorder (OR 1.39 for exposure free vs. exposure); No association with MMR, as pervasive developmental disorders increased while MMR vaccination rates decreased (OR 1.10)</p>	<ul style="list-style-type: none"> • Children with a PPD diagnosis were identified by school officials and this diagnosis was not verified by direct assessment • Individual immunization data was not available 	<p>Excluded</p> <p>-Study did not have an unvaccinated control group as individual immunization data was not available</p>
<p>6. Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-</p>	<p>Objective: To evaluate the effects of MMR immunization and mercury from thimerosal-containing vaccines on the prevalence of autism</p> <p>Methods:</p>	<ul style="list-style-type: none"> • Linear regression coefficients -Prevalence of autism in relation to average mercury doses -Number of doses of primary pediatric 	<p>Close correlation between mercury doses from thimerosal-containing vaccines and prevalence of autism; Potential correlation between MMR vaccines and the</p>	<ul style="list-style-type: none"> • Examined cohorts of children and did not look at individuals therefore can only detect large universal effects • Evidence to support association with MMR vaccine 	<p>Excluded</p> <p>-Study did not have an unvaccinated control group</p>

Appendix B (Continued)

<p>containing childhood vaccines on the population prevalence of autism. <i>Med Sci Monit.</i> 2004;10(3): P133-P139.</p>	<p>Retrospective cohort study of the Biological Surveillance Summaries of the CDC, the US Department of Education dataset and the CDC's yearly live birth estimates</p>	<p>MMR vaccine to the prevalence of autism</p> <ul style="list-style-type: none"> • Odds Ratios from average increased mercury exposure received from thimerosal-containing vaccines 	<p>prevalence of autism</p>	<p>is lacking (OR are not reported)</p>	
<p>7. Geier DA, Geier MR. Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis. <i>Int J Toxicol.</i> 2004;23(6): 369-376.</p>	<p>Objective: To determine if the previously observed effect between thimerosal-containing childhood vaccines and neurodevelopmental disorders are still present after children have had time to further mature</p> <p>Methods: Cohort study of children receiving thimerosal-containing vaccines to those not receiving thimerosal-containing vaccines from 1997 to 2000</p>	<ul style="list-style-type: none"> • Odds ratio for development of neurodevelopmental disorders 	<p>Significantly increased OR for developmental disorders for autism (OR 1.8), mental retardation (OR 2.6), speech disorder (OR 2.1), personality disorder (OR 2.6) and thinking abnormality (OR 8.2)</p>	<ul style="list-style-type: none"> • Limitations of the Vaccine Adverse Events Reporting Dataset include: underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes, and lack of precise denominators • Study of DTaP vaccine and not MMR 	<p>Excluded -Study exposure does not include MMR vaccination</p>

Appendix B (Continued)

<p>8. Goldman GS, Yazbak FE. An investigation of the association between MMR vaccination and autism in Denmark. <i>Journal of American Physicians and Surgeons</i> 2004;9(3): 70-75.</p>	<p>Objective: To compare the prevalence of autism in the periods preceding and following the introduction of the MMR vaccine in Denmark</p> <p>Methods: Cohort study using data from nationwide computerized registration system in Denmark</p>	<ul style="list-style-type: none"> • Linear regression on the prevalence of autism by age cohorts • Relative Risk of autism (adjusted for greater diagnostic awareness) 	<p>RR of autism following introduction of MMR vaccine is 8.5 and adjusted risk is 4.7; suggests a temporal association between the introduction of the MMR vaccine and the rise in autism</p>	<ul style="list-style-type: none"> • The 20-24 year old cohort potentially could have received the monovalent vaccine as toddlers and the MMR booster dose when it became available • Adjusted RR is highly sensitive to the increasing trend during 3 years, 1990 to 1992 	<p>Included</p>
<p>9. Hilton S, Hunt K, Petticrew M. MMR: marginalized, misrepresented and rejected? Autism: a focus group study [abstract]. <i>Arch Dis Child</i> 2007; 92: 322-327.</p>	<p>Objective: To explore how the MMR vaccine controversy impacted the lives of parents caring for children with autism</p> <p>Methods: Qualitative focus group study conducted in the UK</p>	<ul style="list-style-type: none"> • Parent's perception of the MMR vaccine and their response to the controversy surrounding the vaccine and autism 	<p>Many parents felt the vaccine could be too potent for children who are susceptible to developing autism; Many felt guilty that they may have contributed to their child's autism</p>	<ul style="list-style-type: none"> • Non-experimental design (focus group study) 	<p>Excluded -Study does not have an unvaccinated control group (non-experimental design)</p>

Appendix B (Continued)

<p>10. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. <i>J Child Psychol Psychiatry</i> 2005;46(6): 572-579</p>	<p>Objective: To compare autism frequency before and after the termination of the MMR vaccination program</p> <p>Methods: Analysis of annual trends in autism spectrum disorder incidence in Japan</p>	<ul style="list-style-type: none"> • MMR vaccination rates and the corresponding incidence of autism cases • Risk factor analysis using logistic regression 	<p>The incidence of autism increased in birth cohorts both before and after MMR vaccinations were discontinued; statistically significant increase in autism incidence after the discontinuation of the MMR vaccination program</p>	<ul style="list-style-type: none"> • In Japan children only receive one dose of MMR as opposed to the initial vaccination and a booster shot as is the custom in most countries • Provides epidemiological data on the effect of the removal of the MMR vaccine (hypothesized offending agent) 	<p>Included</p>
<p>11. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. <i>JAMA</i> 2003; 290(13): 1763- 1766.</p>	<p>Objective: To determine whether vaccination with a thimerosal-containing vaccine is associated with development of autism</p> <p>Methods: Cohort study of all children born in Denmark from 1990 to 1996 comparing children vaccinated</p>	<ul style="list-style-type: none"> • RR for autism and other autistic-spectrum disorders, including trend with dose of ethylmercury 	<p>Risk of autism did not differ significantly between children vaccinated with thimerosal-containing vaccines and those without (RR 0.85 for autism; RR 1.12 for autistic-spectrum disorders)</p> <p>No evidence of a dose response (RR</p>	<ul style="list-style-type: none"> • Examined children vaccinated with a thimerosal-containing formulation of the pertussis vaccine compared with pertussis vaccine without thimerosal 	<p>Excluded -Study exposure does not include MMR vaccination</p>

Appendix B (Continued)

	with a thimerosal-containing vaccine and a thimerosal-free vaccine formulation		0.98)		
12. Kaye JA, Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. <i>BMJ</i> 2001;322: 460-463.	<p>Objective: To estimate the changes in the risk of autism and assess the relation of autism to the MMR vaccine</p> <p>Methods: Time trend analysis of data from the UK general practice research database (GRPD)</p>	<ul style="list-style-type: none"> Annual and age specific incidence for first recorded diagnosis of autism and coverage rates for the MMR vaccine 	<p>Incidence of autism increased sevenfold in the birth cohorts, while the vaccine coverage rate remained above 95%; Suggests no association between MMR vaccine and autism incidence</p>	<ul style="list-style-type: none"> Initially intended to do a case-control study, but only 3% of cases and controls were not vaccinated Did not obtain and evaluate full clinical record information from general practitioners to describe more fully the characteristics of children diagnosed with autism 	<p>Excluded</p> <p>-Study does not contain an unvaccinated control group</p>

Appendix B (Continued)

<p>13. Madsen KM, Vestergaard M. MMR vaccination and autism: What is the evidence for a causal association? <i>Drug Safety</i> 2004;27(12): 831-840.</p>	<p>Objective: To study the evidence on MMR vaccines and the occurrence of autism with particular focus on the epidemiological literature</p> <p>Methods: Literature review</p>	<ul style="list-style-type: none"> • Case series • Case-control studies • Ecological studies • Cross-sectional studies • Cohort studies 	<p>Review of the literature does not support a causal relationship between MMR vaccines and autism; No primates models exist and the biologic plausibility remains questionable</p>	<ul style="list-style-type: none"> • Literature review that identified 10 epidemiological studies with none reporting a causal association 	<p>Excluded -Study does not contain an unvaccinated control group</p>
<p>14. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. <i>N Eng J Med.</i> 2002;347(19): 1477-1482.</p>	<p>Objective: To evaluate the hypothesized association of MMR vaccine and autism</p> <p>Methods: Retrospective cohort study of all children born in Denmark from January 1991 to December 1998</p>	<ul style="list-style-type: none"> • Relative risk of autistic disorder 	<p>The RR of autistic disorder was 0.92 and the RR of another autism-spectrum disorder was 0.83; strong evidence against a causal association</p>	<ul style="list-style-type: none"> • Exposure data was collected prospectively, independent of parental recall and before the diagnosis of autism • Assumed that the data on MMR vaccination is complete because practitioners in Denmark are reimbursed only after reporting immunizations to the National Board of Health 	<p>Included</p>

Appendix B (Continued)

<p>15. Makela A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. <i>Pediatrics</i> 2002;110: 957-963.</p>	<p>Objective: To assess whether an association prevails between MMR vaccination and encephalitis, aseptic meningitis and autism</p> <p>Methods: Retrospective cohort study of individual MMR vaccination data from a hospital discharge register of children vaccinated between November 1982 and June 1986</p>	<ul style="list-style-type: none"> • Total number of hospitalizations for autism after MMR vaccination during the study period • Number of events within 3 month risk intervals post-vaccination compared with the number expected for encephalitis and aseptic meningitis 	<p>Did not detect any clustering of hospitalizations for autism after vaccination; Did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, and autism</p>	<ul style="list-style-type: none"> • Follow-up was extended to the end of the study for each child vaccinated because of the undefined latency of disease • Authors did not have access to outpatient records and not all autism cases are treated as inpatients • Exact incidence of autism could not be determined because autism develops subtly over long periods of time and some patients may be effected at birth but not symptomatic until later in life 	<p>Excluded -Study did not have an unvaccinated control group</p>
<p>16. Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and</p>	<p>Objective: To assess the quality of evidence assessing a potential association between thimerosal-containing vaccines and autism</p>	<ul style="list-style-type: none"> • 10 epidemiological studies and 2 pharmacokinetic studies of ethylmercury 	<p>Studies do not demonstrate a link between thimerosal-containing vaccines and autism, and the pharmacokinetics of ethylmercury make</p>	<ul style="list-style-type: none"> • Results of epidemiological studies have several inherent limitations such as: differences in study population, multiple potential 	<p>Excluded -Study does not have an unvaccinated control group</p>

Appendix B (Continued)

<p>autism spectrum disorder: a critical review of published original data. <i>Pediatrics</i> 2004;114: 793-804.</p>	<p>Methods: Literature review of original published articles from 1996 to 2004</p>		<p>such an association less likely</p>	<p>sources of bias, and the potential effects of confounding</p>	
<p>17. Patja A, Davidkin I, Kurki T, et al. Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. <i>Pediatr Infect Dis J.</i> 2000;19(12): 1127-1134.</p>	<p>Objective: To distinguish events having a causal relation with MMR vaccination from those with only a temporal relation</p> <p>Methods: Prospective follow-up study using a passive surveillance system launched by the Finnish National Board of Health</p>	<ul style="list-style-type: none"> • Serious adverse events following MMR vaccination (no time frame was imposed) 	<p>30 cases of anaphylaxis were reported and febrile seizures were the most commonly reported event; There were no cases of autism associated with MMR vaccination during the 14 year period</p>	<ul style="list-style-type: none"> • Lack of a control group due to a near fully vaccinated population • The 14 year follow-up allows for ample time to identify cases of autism in the 3 million vaccine doses 	<p>Excluded -Study does not have an unvaccinated control group</p>

Appendix B (Continued)

<p>18. Richler J, Luyster R, Risi S, et al. Is there a 'regressive phenotype' of autism spectrum disorder associated with the measles-mumps-rubella vaccine? A CPEA study. <i>J Autism Dev Dis</i> 2006; 36(3): 299-316.</p>	<p>Objective: To assess whether a new phenotype of regressive autism is present and to assess the association with MMR vaccination</p> <p>Methods: A multi-site case-control study using data collected from 10 sites across the US as part of the Collaborative Program for Excellence in Autism (CPEA)</p>	<ul style="list-style-type: none"> Analyses from the initial ADI-R and algorithm scores from the most recent ADI-R and ADOS as well as standard scores from the Vineland Adaptive Behavior Scales and verbal and non-verbal IQ scores 	<p>Findings of present study provides no evidence that regression in autism is associated with MMR vaccination; Much like children with autism in general, children with autism and regression are a heterogeneous group with varying trajectories of development</p>	<ul style="list-style-type: none"> Children with autism and regression should have more social and communicative skills prior to loss but still show signs of atypical early development Children with regressive autism should show different outcomes in terms of social and communicative skills If regressive autism is associated with GI symptoms, then regressive autism patients should have more GI disorders/symptoms than normal autism patients Age at onset of autistic symptoms should more closely follow age at MMR vaccination Limitation was 	<p>Excluded</p> <ul style="list-style-type: none"> -Study endpoints do not allow for the calculation of a RR or OR for the association of MMR and autism
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Appendix B (Continued)

				that information about child's early development was provided by retrospective parent report, which is open to bias	
19. Smeeth L, Hall AJ, Fombonne E, et al. A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology. <i>BMC Public Health</i> 2001; 1:2.	<p>Objective: To determine if autistic children are more likely to have received MMR vaccination prior to disease onset and to examine whether there is any association between clinical onset of disease and the timing of MMR vaccination</p> <p>Methods: A matched case-control study using data derived from the UK General Practice Research Database</p>	<ul style="list-style-type: none"> • Conditional logistic regression to assess the association between MMR vaccination and autism (Odds ratio) • Case series analyses to estimate the relative incidence of autism in defined time intervals after vaccination 	No results reported	<ul style="list-style-type: none"> • Copies of all hospital summaries will be requested to validate the diagnosis of autism 	Excluded -Study does not allow for the calculation of an OR or RR for the association of MMR and autism

Appendix B (Continued)

<p>20. Smeeth L, Cook C, Fombonne E, et al. MMR vaccination and pervasive developmental disorders: a case-control study. <i>Lancet</i> 2004;364: 963-969.</p>	<p>Methods and objectives described above</p>	<p>Described above</p>	<p>The OR for the association between MMR and pervasive developmental disorder was 0.86 (0.68-1.09) suggesting no association between MMR vaccination and increased risk of pervasive developmental disorders</p>	<ul style="list-style-type: none"> • Case reports were obtained for 87% of patients to validate the diagnosis of a pervasive developmental disorder • Limitation was that when children joined a participating general practice after the date of MMR vaccination, their previous vaccination history was recorded retrospectively 	<p>Included</p>
<p>21. Takahashi H, Suzumura S, Shirakizawa F, et al. An epidemiological study of Japanese autism concerning routine childhood immunization history. <i>Jpn J Infect Dis.</i> 2003;56: 114-117.</p>	<p>Objective: To assess the causal association of autism with the MMR vaccine</p> <p>Methods: A case-control study of adjusted logistic regression analysis on subjects growing up in the Tokyo area between 1988 and</p>	<ul style="list-style-type: none"> • Logistic regression analysis (Odds ratio) 	<p>The OR for monovalent measles immunization (OR 5.33), non-mumps immunization (OR 8) and non-rubella immunization (OR 8.57) with the development of autistic spectrum disorders; Suggests a decreased risk of</p>	<ul style="list-style-type: none"> • Only 21 cases were enrolled in the study • Results may be biased by the informed consent process, which may have discouraged caregivers from enrolling children with a poor or incomplete immunization history • Compared 	<p>Excluded -Study did not have an unvaccinated control group</p>

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	1992		autism with MMR vaccines compared with monovalent antigens	MMR vaccine to monovalent antigens	
22. Taylor B. Vaccines and the changing epidemiology of autism. <i>Child Care Health Dev</i> 2006;32(5): 511-519.	<p>Objective: To review the available literature on the association between autism and MMR vaccination</p> <p>Methods: Literature review and interpretation</p>	<ul style="list-style-type: none"> • Interpretation of published studies on the association between autism and MMR vaccination 	The recorded prevalence of autism has increased considerably in recent years. The strong genetic component makes a post-natal cause unlikely	<ul style="list-style-type: none"> • Diagnostic procedures for determining special educational disabilities such as autism are not standardized nor have they been uniform over time 	Excluded -Study did not have an unvaccinated control group
23. Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. <i>Lancet</i> 1999; 353: 2026-29.	<p>Objective: To investigate whether MMR vaccine may be causally associated with autism</p> <p>Methods: Epidemiological study of children born with autism since 1979 in the UK using the case-series method to investigate the clustering of onsets in the post vaccination period</p>	<ul style="list-style-type: none"> • Time trend analysis • Relative risk of temporal association of autism and MMR vaccination • Case series for temporal association 	Steady increase in cases by year of birth with no sudden step up or change in trend line; no temporal association between autism onset with one or two years of MMR vaccination (0.94, 1.09)	<ul style="list-style-type: none"> • Diagnosis of autism was confirmed based on medical records • Limitation was not that the diagnosis could not be verified in all cases and the ascertainment may have been incomplete • Clinical notes were of variable quality and many did not contain updated information 	Included

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<p>24. Taylor B, Miller E, Lingam R, et al. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. <i>BMJ</i> 2002;324: 393-396.</p>	<p>Objective: To investigate whether MMR vaccination is associated with bowel problems and developmental regression in children with autism</p> <p>Methods: Population study with case note review to independently recorded vaccine data</p>	<ul style="list-style-type: none"> • Recorded bowel problems lasting at least three months, age of reported regression and relation to MMR vaccination • Single and multivariate logistic regression 	<p>The proportion of children with developmental regression (OR 0.98) or bowel symptoms did not change significantly during the 20 years from 1979; findings provide no support for an MMR associated “new variant” form of autism with developmental regression and bowel problems</p>	<ul style="list-style-type: none"> • The percentage of patients with regression (25%) is likely an overestimation • Limitation was that data were not recorded systematically and there was variability in the level of detail 	<p>Included</p>
<p>25. Thompson WW, Price C, Goodson B, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. <i>N Engl J Med.</i> 2007; 357(13): 1281-1292.</p>	<p>Objective: To assess the association between current neuropsychological performance and exposure to mercury during the prenatal period, postnatal period, and the first 7 months of life</p> <p>Methods: Cohort</p>	<ul style="list-style-type: none"> • Neuropsychological outcomes associated with thimerosal (mercury) exposure • Measures of association measured with ordinary least-squares regression and logistic regression 	<p>Only a few significant associations with exposure to mercury from thimerosal were found; the detected associations were small and almost equally divided between positive and negative effects</p>	<ul style="list-style-type: none"> • Study did not assess autism-spectrum disorders • Mercury exposure was determined based on published data and the data from the FDA on the vaccines that the children received, from HMO records, immunization records, 	<p>Excluded -Study exposure did not include MMR vaccination</p>

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	study of 1047 children between the ages of 7 and 10 years administered standardized tests assessing 42 neuropsychological outcomes			and maternal interview <ul style="list-style-type: none"> • Limitations include a potential selection bias due to a majority of selected families declining to participate and the inability to control for interventions such as speech therapy that may have biased results toward the null 	
26. Uchiyama T, Kurosawa M, Inaba Y. MMR vaccination and regression in autism spectrum disorders: negative results presented from Japan. <i>J Autism Dev Disord</i> 2007;37: 210-217.	<p>Objective: To investigate whether the MMR vaccination is associated with “regressive autism”</p> <p>Methods: Case-control comparison of children who received and did not receive the MMR vaccination and the change over time in the proportion of children who showed regressive symptoms across the pre-MMR, MMR and post-MMR</p>	<ul style="list-style-type: none"> • Odds ratio for the association between regression and MMR exposure 	The OR for those in the MMR group who received the vaccine was 0.744 (0.349-1.517); The odds ratio for children who did not receive the vaccine across the three generations was 0.626 (0.323-1.200); the rate of regression did not vary across the pre-MMR, the MMR and the post-MMR cohorts	<ul style="list-style-type: none"> • In Japan the MMR vaccine was only given between 1985 and 1991 and thus allows for comparison of the before, during, and after effect of MMR vaccination • Assumed that information in the Maternal and Child Handbook was accurate as most of the information is entered by health professionals • Limitations: 	Included

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	time frames in Japan			study conducted in one private clinic, the sample size of subjects who received the MMR vaccine was small, and several issues concerning definition and measurement of regression (information was highly dependant on parental report using an instrument which asks limited questions on regression)	
27. Wakefield AJ, Murch SH, Linnell J, Casson DM, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. <i>Lancet</i> 1998;351: 637-641.	<p>Objective: To investigate a series of children presenting with chronic enterocolitis and regressive developmental disorder following vaccination with the MMR vaccine</p> <p>Methods: Consecutive series</p>	<ul style="list-style-type: none"> • Temporal association between symptom onset and vaccination 	In 8 of the 12 children the onset of behavioral problems was linked to MMR vaccination by the parent or child's physician; Once child received the monovalent measles vaccine after which his development slowed	<ul style="list-style-type: none"> • Potential selection bias in self-referred group • Small sample size (12 children) • Lack of control group • Temporal association largely depends on parent recall and when they first notice signs of developmental 	Excluded -Study did not have an unvaccinated control group

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	analysis of 12 children with chronic enterocolitis and regressive developmental disorder			regression	
28. Wilson K, Mills E, Ross C, et al. Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine. <i>Arch Pediatr Adolesc Med.</i> 2003;157: 628-634.	<p>Objective: To systematically review the evidence for and against the existence of an association between autistic spectrum disorder and the MMR vaccine</p> <p>Methods: Systematic review of medical literature to identify all controlled epidemiological articles examining the association between autistic spectrum disorder and MMR vaccination</p>	<ul style="list-style-type: none"> • 12 epidemiological studies assessing the association between autistic spectrum disorder and MMR vaccination 	The results of all of the studies showed no association between autistic spectrum disorders and the MMR vaccine	<ul style="list-style-type: none"> • Studies included: case-series, cross-sectional studies, case-control studies, and retrospective cohort studies • Studies varied in how autistic spectrum disorder was diagnosed 	Excluded -Study did not have an unvaccinated control group

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<p>29. Woo EJ, Ball R, Bostrom A, et al. Vaccine risk perception among reporters of autism after vaccination: vaccine adverse event reporting system 1990-2001. <i>Am J Public Health</i> 2004; 94(6): 990-995.</p>	<p>Objective: To investigate vaccine risk perception among reporters of autism to the Vaccine Adverse Event Reporting System (VAERS)</p> <p>Methods: Structured interviews were conducted of 124 patients who reported autism to VAERS between 1990 and 2001 compared to published survey results of parents in the general population</p>	<ul style="list-style-type: none"> • Perceptions of parents of children with autism who believe that vaccinations may have been a cause 	<p>Only 15% deemed immunizations extremely important for children’s health; two-thirds had withheld vaccines from their children</p>	<ul style="list-style-type: none"> • Passive surveillance systems such as VAERS are subject to many limitations including: underreporting, incomplete information, inadequate denominator data, and lack of an unbiased comparison group 	<p>Excluded -Study did not allow for the calculation of an OR or RR for the association between autism and MMR</p>
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