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Vaccines and Autism – An Unlikely Connection

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1. Introduction

Autism spectrum disorders (ASDs) encompass a group of chronic developmental disorders characterized by repetitive or stereotypic behaviors, interests and activities, along with marked impairments in a child's ability to socialize and communicate. These debilitating conditions impact every aspect of the life of a child and his/her family. Modern advances in science and technology have provided successful explanations and interventions for many previously life-threatening conditions such as bacterial meningitis and extreme prematurity. However, a scientific cause or definitive treatment for ASDs remains elusive. This lack of evidence regarding the biological causes of ASDs and successful, standardized treatment modalities challenges both parents/caregivers and health care providers in their understanding of these conditions, and effectively addressing the needs of this pediatric population. In some instances, the lack of evidence has fueled the development of hypotheses and possible associations based on the publication of case reports and small cohort studies.

The prevalence of ASDs has increased over the past several decades, but it is unclear whether this is due to a true increase, increasing awareness, or differences in the methods used to diagnose these conditions and assess their prevalence. Given the irrefutable increase in the prevalence of ASDs, there has been interest in both genetic influences and environmental exposures that may have led to this increase over the past several decades. Although a small proportion of ASDs are associated with known congenital conditions, and several genes involved in ASDs have been identified, in most cases the etiology of ASDs is unknown. Some of the environmental triggers for ASDs that have been postulated include lack of breastfeeding, supplemental feeding with infant formulas that do not contain docosahexaenoic acid and arachidonic acid supplementation, childhood vaccinations, the use of acetaminophen and other analgesics, certain viral infections, and sundry other environmental exposures. Among these exposures, vaccinations have received the most widespread interest and attention by both the lay public as well as the medical and scientific communities. Young children are receiving more vaccines than ever, with multiple vaccines given at each visit, to provide protection against a plethora of infectious diseases. ASDs are often diagnosed in children at about the same chronologic age as the peak time for vaccine delivery. Unfortunately, a small, but vocal minority of people have attributed the rise in rates of ASDs to the increase in childhood vaccinations, despite the lack of rigorous scientific evidence to support this contention. The question about vaccines and ASDs continues to cause conflict between public health authorities

and worried parent groups. This chapter will provide further details of the arguments on both sides and an analysis of the scientific evidence that supports the view that ASDs and vaccines are unlikely to be linked.

2. Vaccines - victims of their own success?

Vaccination is among the greatest achievements of modern medicine, leading to the eradication of naturally occurring smallpox and the near elimination of polio [1]. Most of the lay public as well as many scientists and physicians do not realize that the first vaccines against smallpox and rabies proved their effectiveness even before the identification of viruses as infectious agents [2]. Vaccination has a short history in medicine and public health when measured against the centuries during which human beings have fought desperately to prevent and treat various plagues and pestilences. Routine vaccination of large populations is a phenomenon of the 20th century [3]. Despite its relatively recent entry into the field of medicine and public health, vaccination has helped in the world-wide eradication/control of 12 major infectious diseases, including smallpox, diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b disease, poliomyelitis, measles, mumps, rubella, typhoid and rabies [3]. In the United States, vaccination has contributed to the significant decline in morbidity from nine vaccine-preventable diseases and their complications between 1900 and 1999 (Table 1) [4]. Vaccines have been described as the single most life-saving accomplishment of the 20th century [5].

Disease	Baseline 20th century annual morbidity	1998 Provisional morbidity	% Decrease
Smallpox	48,164	0	100%
Diphtheria	175,885	1	100%
Pertussis	147,271	6,279	95.7%
Tetanus	1,314	34	97.4%
Poliomyelitis (paralytic)	16,316	0	100%
Measles	503,282	89	100%
Mumps	152,209	606	99.6%
Rubella	47,745	345	99.3%
Congenital rubella syndrome	823	5	99.4%
Haemophilus influenzae type b	20,000	54	99.7%

Table 1. Baseline 20th century annual morbidity and 1998 provisional morbidity from nine diseases with vaccines recommended before 1990 for universal use in children - United States

Parents and many health care providers of the 21st century, particularly in more developed areas of the world such as the United States and Western Europe, have limited or no experience with the devastating effects of these diseases. In the United States public health

officials now recommend 28 to 31 vaccine doses before the age of 18 years, many of which are administered together to provide protection early in life, for the convenience of families and health care providers, and to decrease distress to the infant. Public health experts recommend that 95% of the population be vaccinated to provide herd immunity and minimize the possibility of resurgence of these deadly infections. However, parents in developed countries who have not seen these diseases or their disastrous consequences sometimes feel that they are being pressured into immunizing their children involuntarily for public good rather than personal benefit [6]. Some parents even perceive a greater risk to their children from vaccination than from the diseases themselves, not recognizing that the threat from these diseases is reduced simply because we do have effective vaccines to prevent them. Vaccination has thus regrettably become a polarized issue with some parents stressing their own child's well-being at the one extreme and health experts advocating for public health outcomes on the other extreme.

3. Genesis of the "vaccines cause autism" theory

One of the first claims that vaccines might cause autism was made in a book entitled "A Shot in the Dark" by Harris L. Coulter and Barbara Loe Fisher [7]. In it the authors wrote, "With the increasing number of vaccinations American babies have been required to use has come increasing numbers of reports of chronic immune and neurologic disorders … including … autism." At the time, little attention was paid to this assertion. The hypothesis received far greater support after a British physician and researcher Dr. Andrew Wakefield along with 12 co-authors published an article describing abnormal gastrointestinal features among 12 children who had been referred to their university pediatric gastroenterology clinic [8]. All of the children were reported to have some type of developmental disorder, and 9 of them had been diagnosed with autism. In 6 of these 9 children, either the parent or a physician had linked the onset of developmental regression with the receipt of the MMR vaccine. In this paper, Wakefield *et al*. proposed an elaborate sequence of events: that measles virus from the live-attenuated MMR vaccine caused intestinal inflammation, the inflamed intestines became "leaky", allowing undefined harmful proteins to enter the bloodstream, travel to the brain and cause autism. In 2000, Wakefield and colleagues published a second paper in which white blood cells in the same 9 autistic children (with what was now referred to as "autistic enterocolitis") were examined for the presence of measles virus [9]. Using polymerase chain reaction, the authors reported that measles virus RNA fragments were found in 3 out of the 9 children, but in none of 22 controls, lending credence to the "leaky-gut" theory [9].

Additional theories of the putative association between vaccines and ASDs include:

1. Concern about the mercury-containing preservative thimerosal (which was used in childhood vaccines for many years) and its potential toxic effects on the developing central nervous system in children;
2. Worry that a combination of MMR and thimerosal-containing vaccines produces additive or synergistic toxic insults on children's brains;
3. Apprehension related to the simultaneous administration of multiple vaccines which might "overwhelm" or "weaken" the relatively immature immune system in young children.

   These theories will be explored later in this chapter, but let us first further discuss the most well-known controversy surrounding vaccines and ASDs.

4. Impact of the "MMR causes autism" scare

As a consequence of the publications by Wakefield and his colleagues, many parents anxious about the risk of autism, particularly in the UK, began to refuse the MMR vaccine for their children. After the controversy began, the MMR vaccination compliance dropped in the UK from 92% in 1996 to 82% in 2002 [10]. In some parts of London, it was as low as 62% in 2003, far below the rate needed to avoid an epidemic of measles [10]. By 2006, coverage for MMR for children at 24 months of age in the UK was 85%, significantly lower than the 94% coverage rate for other vaccines [11]. Predictably, the fall in vaccination rates for MMR vaccine was followed by an increase in the incidence in the UK of two of the three diseases that are prevented by it. In 1998 there were 56 confirmed cases of measles in the UK. By the first five months of 2006, there were 449 cases of measles reported in the UK, with the first death since 1992. As expected, the cases occurred in inadequately vaccinated or unvaccinated children [12].

Mumps cases also began rising in 1999 after many years, and by 2005 the UK was in the midst of a mumps epidemic with almost 5000 reports in the first month of 2005 alone [13]. A total of 56,390 notified cases of mumps were reported in England and Wales that year [14]. Interestingly, most patients were aged between 15 and 24 years, too old to have received the routine MMR vaccine around the time the paper by Wakefield *et al.* was published, and too young to have contracted natural mumps as a child. With the decline in mumps that followed the introduction of the MMR vaccine in the UK, these individuals had not been exposed to the disease, and therefore had no immunity, either natural or vaccine-induced. Once immunization rates began to decline following the controversy and the disease re-emerged, they were susceptible to infection [14].

Measles and mumps cases continued in 2006, at incidence rates 13 and 37 times greater than their respective 1998 levels [15]. Two children were severely and permanently injured by measles encephalitis in London [16]. Measles outbreaks also resulted in casualties in nearby countries. Three deaths and 1,500 cases of measles were reported in an outbreak in Ireland, which occurred as a direct result of decreased vaccination rates following the MMR scare [16]. Another study reported the hospitalization of 111 cases of measles mostly with pneumonia, tracheitis or dehydration, with 13 of them requiring ICU admission and 7 of the children needing mechanical ventilation [17]. One editorial has described this as the "fallout" of the paper published by Wakefield et al. [18]. In 2008, for the first time in 14 years, measles was declared to be endemic again in the UK. This was caused by the preceding decade's low MMR vaccination rates, which in turn created a population of susceptible children who could spread the disease [15]. MMR vaccination rates for English children remained at 85% in 2007–08, unchanged from the year before and at too low a level to prevent serious measles outbreaks [19]. In May 2008, a British 17-year-old with an underlying immunodeficiency died of measles [15]. In 2008, measles epidemics were reported from Austria, Italy, and Switzerland [15].

In a study conducted in the US, selective MMR nonreceipt, occurring in as few as 0.77% of children in the 1995 cohort, rose to 2.1% according to the 2000 National Immunization Survey [20]. Children included in the 2000 National Immunization Survey were born at around the time that the putative link between MMR and autism surfaced in the medical literature. Sporadic importations of measles into the US had occurred since the disease was declared eliminated from the US in 2000. However, in 2008, a measles outbreak occurred in the US involving 16 states [21]. Of the individuals affected, 94% were US residents, 93% were unvaccinated and 86% of the cases were imported (69% from Europe).

5. Lack of evidence to support the "MMR causes autism" theory

The scientific limitations of the paper published by Wakefield *et al.* [8] were pointed out soon after it first appeared [22]. It was noted that the paper reported on a small series of cases with no controls, linked three common clinical conditions, and relied on the recall and beliefs of parents [23]. Several large population- and ecologic-based studies were conducted over the following decade that consistently found no evidence of a link between the MMR vaccine and autism and failed to provide any support for Wakefield's theory [24-27]. In fact, the lack of an association between MMR vaccination and autism in children is supported by 19 additional scientific studies performed by diverse groups of investigators using various research methodologies involving disparate groups of patients over more than a decade [28-46]. Several of these studies have been discussed in detail in 4 review articles [47-50]. In other words, despite significant efforts by numerous groups of investigators, the findings of Wakefield *et al*. [8] could not be replicated or confirmed. Interestingly, in a case-control study conducted in Poland, where the MMR vaccine was introduced later than in most other European countries, the investigators report that the risk of autism was lower in children who received the MMR vaccine than in those who did not [44]. The authors do not claim a "protective" effect of the vaccine, but correctly recognize that the decreased risk of autism among vaccinated children may have been due to other confounding factors in their health status such as, healthcare workers or parents who may have noticed signs of developmental delay or disease before the actual autism diagnosis and for this reason have avoided vaccination [44]. This type of critical and honest analysis is missing from studies that support the contention that the MMR vaccine is associated with ASDs [51-53].

In 2004, 10 of the 12 coauthors of Wakefield's acknowledged that "no causal link was established between MMR vaccine and autism as the data were insufficient" in their original paper and asked to "formally retract the interpretation" of their findings [54]. Moreover, an investigation by D'Souza *et al*. using a larger sample size than Wakefield and his colleagues' original study [9], failed to reveal persistence of measles virus RNA in the peripheral blood of children with ASDs [55]. Two additional studies reported no detectable measles virus genome sequence in the blood of autistic children who had received MMR vaccination [56, 57]. Further, in a case-control study conducted by Hornig *et al*., ileal and cecal tissues from 25 children in the US with autism and gastrointestinal (GI) disturbances and 13 children with GI disturbances alone (controls) undergoing clinically-indicated ileocolonoscopy, were evaluated by real-time reverse transcription (RT)-PCR for presence of measles virus RNA in three laboratories blinded to diagnosis, including one wherein the original findings suggesting a link between measles virus and ASDs were reported [58]. The authors reported no differences between case and control groups in the presence of measles viral RNA in the ileum and cecum [58].

Despite the scientific difficulty with proving a negative, the Institute of Medicine (IOM) in a report on vaccine safety has stated conclusively that there is no causal relationship between the administration of the MMR vaccine and the onset of ASDs [59]. This eighth and final report of the Immunization Safety Review Committee examined the hypothesis that vaccines, specifically the MMR vaccine and thimerosal-containing vaccines, are causally associated with autism. The committee reviewed the extant published and unpublished epidemiological studies regarding causality and studies of potential biologic mechanisms by which immunizations might cause autism and concluded that the body of epidemiological evidence favored *rejection* of a causal relationship between the MMR vaccine and autism

[59]. The committee further found that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only [59]. Thus, the MMR vaccine continues to be safe, efficacious and recommended by the public health authorities and supported by the vast majority of medical professionals. Nevertheless, despite the large body of scientific evidence to the contrary, Barbara Loe Fisher continues to support her initial theory that vaccines cause autism [60].

6. MMR and autism - honest error or deliberate fraud?

The Office of Research Integrity in the United States defines fraud as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results [61]. They further explain that:

a. Fabrication is making up data or results and recording or reporting them.
b. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
c. Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
d. Research misconduct does not include honest error or differences of opinion.

Editors at the BMJ claim that it has taken the diligent skepticism of one man, Brian Deer, a journalist standing outside the realms of medicine and science, to show that the initial paper by Wakefield *et al.* [8] was in fact an elaborate fraud [62]. In a series of articles published this year, Deer reports on how Wakefield altered numerous facts about his patients' medical histories in order to support his claim to have identified a new syndrome [63]; how his institution, the Royal Free Hospital and Medical School in London, supported him as he sought to exploit the ensuing MMR scare for financial gain [64]; and how key players failed to investigate thoroughly in the public interest when Deer first raised his concerns [65]. Deer published his first investigation into Wakefield's paper in 2004 [66]. This uncovered the possibility of research fraud, unethical treatment of children, and Wakefield's conflict of interest through his involvement with a lawsuit against manufacturers of the MMR vaccine [62]. Building on these findings, the General Medical Council (GMC) of the UK launched proceedings that focused on whether the research conducted by Wakefield *et al.* [8] was ethical.

While the disciplinary panel was examining the children's medical records in public, Deer compared them with what was published in the *Lancet* article. His focus was not on whether the research was ethical, but whether it was factual. Through interviews, documents, and data made public at the GMC hearings as well as his investigations spanning several years, Deer has unearthed clear evidence of falsification in Wakefield *et al.*'s [8] paper. He found that in every one of the 12 cases reported by Wakefield *et al.* [8], there was misrepresentation or undisclosed alteration, and that in no single case could the children's medical records be fully reconciled with the descriptions, diagnoses, or histories published in the article. The editors of the BMJ have questioned the origins of the falsified data and lay the blame squarely upon Andrew Wakefield [62]. They question whether it is possible that he was wrong, but not dishonest: that he was so incompetent that he was unable to fairly describe the project, or to report even one of the 12 children's cases accurately, and conclude that the article resulted not from honest errors, but a deliberate attempt to defraud [62]. They base

their conclusion on the contention that a great deal of thought and effort must have gone into drafting the paper to achieve the results he wanted, since the discrepancies all led in one direction and the misreporting was gross [62].

7. Consequences of the "MMR causes autism" fraud

Nearly 12 years after its original publication, the journal *Lancet* fully retracted the article by Wakefield *et al*., based on several elements of the paper being proven to be false [67]. The GMC completed its longest-ever "fitness to practice" hearing, and based upon it withdrew Dr. Wakefield's license to practice medicine [68]. Andrew Wakefield was branded as being "dishonest," "unethical," and "callous" [69]. His associate Professor John Walker-Smith, the senior clinician in the project, was found to have presided over "high risk" research without clinical indication or ethical approval, and also struck off the medical register [70]. Further details about this controversy and autism research have been published in a couple of recent books [71, 72].

The Wakefield case and its aftermath have resulted in a reevaluation of how biomedical research is regulated. There have been calls for a national Health Research Agency to be established in the UK to oversee the regulation and governance of health research [73]. Others have advocated for public access to raw data, arguing that the apparent discrepancies between the patient records and the data in the article by Wakefield *et al*. [8] might have come to light sooner, perhaps even before publication, had the raw data been available for public scrutiny [74]. Opel et al. propose that as part of an effort to improve research integrity traditional hierarchies and authority gradients need to be bypassed in order to empower everyone in the research enterprise-especially those on the front lines, such as research assistants, data analysts, and project managers-to raise questions and be able to report suspected misconduct without fear of reprisal [75]. They suggest that the ability to investigate research incidents needs to be strengthened using the best tools and techniques available to protect the safety of research subjects [75]. They also assert that the customs and culture around biomedical research need rethinking and reform. They point to the disastrous impact that Wakefield's flawed study has had on vaccine coverage, recrudescence of vaccine-preventable diseases and erosion of the public's trust in science, and exhort rapid action to remedy the current system of ensuring research integrity [75].

Based on the above referenced body of knowledge, few people could deny that Wakefield *et al*.'s paper was fatally flawed both scientifically and ethically, if not outright fraudulent. Unfortunately, an allegation is remembered long after it has been disproved. In a postal survey of parent's decisions, attitudes and use of information about MMR immunization in the UK, Casiday *et al*. report that both MMR-accepting and refusing parents were supportive of immunization, but had a high level of concern about the safety of vaccines [76]. A web-based survey of parents conducted in 2009 in the US, showed that while most parents agreed that vaccines protect their child(ren) from diseases, more than half of the respondents also expressed concerns regarding serious adverse effects of vaccines [77]. Overall, 11.5% of the parents had refused at least 1 vaccine that their doctor had recommended for their child(ren), with 17.7% refusing the MMR vaccine [77]. A quarter of the survey responders either strongly agreed or agreed with the statement "Some vaccines cause autism in healthy children" [77]. Wakefield's legacy promises to live on.

8. Origins of the thimerosal and autism controversy

Another hot button issue that has been debated in relationship to the onset of ASDs is exposure to thimerosal, a preservative that has been present in vaccines since the 1930s [78]. Multidose vaccine vials have the antibacterial agent thimerosal added to preserve the sterility of the contents. Thimerosal contains 49.6% mercury by weight and metabolizes into *ethylmercury* and thiosalicylate. Towards the end of the 20th century, the US government became aware of and concerned about mercury exposure in the general population [79] and the US Environmental Protection Agency (EPA) published standards of safe limits of oral *methylmercury* exposure particularly from fish and shellfish [80, 81]. Statements from the EPA clearly indicate that people in the U.S. are mainly exposed to organic *methylmercury*, when they eat fish and shellfish that contain it. The EPA identifies factors that determine how severe the health effects are from mercury exposure including:

- the chemical form of mercury
- the dose
- the age of the person exposed (the fetus is the most susceptible)
- the duration of exposure
- the route of exposure -- inhalation, ingestion, dermal contact, etc.
- the health of the person exposed.

Various agencies have developed guidelines for "safe" exposure to *methylmercury*, including the EPA [82, 83], U.S. Agency for Toxic Substances and Disease Registry (ATSDR) [84], the U.S. Food and Drug Administration (FDA) [85], and the World Health Organization (WHO) [86]. These exposure levels ranged from 0.1 μg/kg body weight/day (EPA) to 0.47 μg/kg body weight/day (WHO), and while clearly different, were within the same order of magnitude. The various mercury guidelines were based on epidemiological and laboratory studies of *methylmercury*, whereas thimerosal as noted above is a derivative of *ethylmercury*. Because they are different chemical entities i.e. *ethyl* versus *methylmercury,* different toxicological profiles are expected for the two compounds. It should be recognized that there was uncertainty in applying the *methylmercury*-based guidelines to thimerosal. The FDA has noted that these guidelines may be used as screening tools in risk assessment to evaluate the "safety" of mercury exposures, but are not meant to be bright lines above which toxicity *will* occur [87].

In 1997, Frank Pallone, a U.S. congressman from New Jersey, added an amendment to a (FDA) reauthorization bill which gave the FDA 2 years to "compile a list of drugs and foods that contain intentionally introduced mercury compounds and provide a quantitative and qualitative analysis of the mercury compounds in the list" [88]. The bill was signed into law as the FDA Modernization Act of 1997, and garnered little public or press attention at the time. To abide by this law, the FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines in 1999, and notably, found *no evidence of harm* from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions [89]. The maximum cumulative exposure to mercury from vaccines in the recommended childhood immunization schedule at the time, was found to be within acceptable limits for the *methylmercury* exposure guidelines set by FDA, ATSDR, and WHO. However, depending on the vaccine formulations used and the weight of the infant, some infants could have been exposed to cumulative levels of mercury during the first six months of life that exceeded EPA recommended guidelines for safe intake of *methylmercury*.

As more thimerosal-containing vaccines were added to the recommended infant and child immunization schedule, theoretical concerns based on the cumulative amounts of thimerosal that a child was receiving in the first two years of life were raised. As a precautionary measure, the US Public Health Service (USPHS) (which includes the FDA, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA)) and the American Academy of Pediatrics issued two Joint Statements, urging vaccine manufacturers to reduce or eliminate thimerosal in vaccines as soon as possible [90, 91]. This was done through an "abundance of caution," even though there was no evidence that thimerosal-containing vaccines contributed to toxic mercury levels in children, and in fact *ethylmercury* does not have the neurotoxic effects of *methylmercury*. The action taken by the USPHS and AAP had significant, unintended ripple effects on the general public's concerns about vaccine safety in young children. Beginning in 2000, many parents founded advocacy groups based on the belief that thimerosal had caused their children's autism [92]. The birth dose of hepatitis B vaccine which in 1999 contained thimerosal was subsequently withheld from many children and the hepatitis B vaccination campaign in the US experienced a serious setback [93]. Although thimerosal-free hepatitis B vaccines became available shortly thereafter, the effort to vaccinate infants at birth remains a challenge in some areas.

9. Insufficient scientific evidence linking thimerosal with autism

The signs and symptoms of autism are clearly distinct from those of mercury poisoning. Children with mercury poisoning show characteristic motor, speech, sensory, psychiatric, visual, and head circumference changes that are fundamentally different from those of or absent in children with autism. Concerns about mercury as a cause of autism therefore seemed biologically implausible [94]. Nevertheless, it began to be suggested that there may be adverse neurological effects including autism due to *ethylmercury* exposure from the use of thimerosal in vaccines [95-103]. Notably, most of the studies that reported an association of thimerosal with neurodevelopmental disorders including autism were performed by the same group of researchers [98-103], using the Vaccine Adverse Events Reporting System (VAERS) as their data source. The VAERS is a passive reporting system to which anyone can report adverse events that are purported to be associated with vaccines. Goodman and Nordin have shown that most reports to the VAERS system in recent years regarding thimerosal were influenced by litigation, and are therefore unsuitable for scientific study [104]. In other words, most of the adverse reports regarding thimerosal and autism were related to pending lawsuits for vaccine injury. This severely biased the dataset, and it should not have been used to assign causality.

Meanwhile, several other studies performed by various groups of researchers did not support the postulated association between thimerosal and ASDs [33, 105-112]. Three ecological studies were performed in 3 different countries comparing the incidence of autism with thimerosal exposure from vaccines [33, 109, 110]. In each case, thimerosal had been removed from childhood vaccines, allowing robust comparisons of vaccination with thimerosal-containing and thimerosal-free products. A large study from Denmark showed no difference in the incidence of autism among children who had received vaccines containing different amounts of thimerosal [109]. Despite the removal of thimerosal from vaccines in 1992 in Sweden and Denmark, the incidence of autism increased steadily from 1990 to 2000 [110]. Thimerosal exposure and pervasive developmental disorder diagnosis

were found to be independent variables in a study from Canada [33]. In this study, the highest rates of pervasive developmental disorder were found in children who had received thimerosal-free vaccines [33].

Additional epidemiologic studies also failed to show any association between thimerosol exposure and ASDs. In a large study from Denmark, researchers found that the risk of autism did not differ between children vaccinated with thimerosal-containing vaccines and those vaccinated with thimerosal-free vaccines or between children who received larger or smaller quantities of thimerosal [107]. They also reported that the rates of autism increased after the removal of thimerosal from all vaccines. In the United States, researchers at the CDC used the Vaccine Safety Data Link to examine the health records of 140,887 children born during 1991–1999, including over 200 children diagnosed with autism [111]. They found no relationship between receipt of thimerosal-containing vaccines and autism. In a large study conducted in the UK, researchers evaluated the vaccination records of 100,572 children born during 1988–1997, 104 of whom were affected with autism [105]. No relationship between thimerosal exposure and developmental disorders was observed. In a separate study from the UK, researchers prospectively followed 12,810 children born during 1991–1992, for whom they had complete vaccination records, and again found no relationship between early thimerosal exposure and subsequent adverse neurological or psychological outcomes [106].

A long-term follow-up study by the CDC showed that early thimerosal exposure from vaccines did not cause adverse neuropsychological outcomes after 7-10 years [113]. In another long-term follow-up study performed in Italy, 2 groups of children with exposure to different doses of thimerosol were examined [114]. Among the 24 neuropsychological outcomes that were evaluated, only 2 were significantly associated with thimerosal exposure. The authors noted that due to the large number of statistical comparisons performed, the few associations found between thimerosal exposure and neuropsychological development might be attributable to chance [114]. The associations found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance could not be determined. A case-control study was conducted in 3 managed care organizations (MCOs) in the US that included 256 children with ASD and 752 matched controls [115]. The authors report that in their study, prenatal and early-life exposure to *ethylmercury* from thimerosal-containing vaccines and immunoglobulin preparations was not related to increased risk of ASDs [115]. Several scientific and public policy review committees have carefully evaluated the existing data and concluded that there was not sufficient evidence of a link between autism and thimerosal in vaccines [59, 87, 116]. In fact, the Institute of Medicine's 2004 evaluation included a strong statement that rejected the idea that thimerosal-containing vaccines cause autism, concluding that "…epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism" [116].

Interestingly, comparisons of *methylmercury* and *ethylmercury* tissue distribution following exposure in young mice [117] and monkeys [118] both reported significantly less mercury deposited in the brain following *ethylmercury* or thimerosal exposure, as compared to *methylmercury* exposure. The authors of these studies concluded that the clearance and tissue distribution of the two compounds differ significantly in animal models [117, 118]. The route of exposure (injection versus ingestion) to *methylmercury* also resulted in differences in

the amount of mercury deposited in the brain in mice, with exposure via intramuscular injection resulting in *less* mercury deposition than via ingestion [117]. In a study by Pichichero ME, *et al*., mercury levels in blood and other samples from infants who had received routine immunizations with thimerosal-containing vaccines were measured [119]. Blood levels of mercury did not exceed safety guidelines for *methylmercury* for all infants in this study. Further, mercury was cleared from the blood in infants exposed to thimerosal faster than would be predicted for *methylmercury*. Infants excreted significant amounts of mercury in stool after thimerosal exposure, thus removing mercury from their bodies. These results suggest that there are differences in the way that thimerosal and *methylmercury* are distributed, metabolized, and excreted. Thimerosal appears to be removed from the blood and body more rapidly than *methylmercury* in young children. Due to the differences in the biological behavior of these two compounds, the flaws in extrapolating the risk assessment of thimerosal by direct comparison with *methylmercury* are well described in a review by Aschner and Ceccatelli [120]. Another review article summarizes the studies investigating thimerosal exposure and the development of ASDs (Table 2) [121].

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

Table 2. Studies Investigating Thimerosal Exposure with Autism and Other Developmental Outcomes.

Thimerosal has been removed from all childhood vaccines in the US, but this has also increased production costs which are ultimately passed on to the consumer. Only some preparations of influenza vaccine still contain thimerosal (See Table 3). However, largely unfounded concerns about the adverse effects of thimerosal have made many parents reluctant to have their children receive this vaccine. What goes unrecognized by the lay public and even many health care providers is that influenza virus causes hundreds of thousands of hospitalizations and an average of 100 deaths among children every year. Mistakenly attempting to protect their children from a theoretical risk, these parents inadvertently place them at the real risk of being hospitalized or killed by influenza. An alarming recent trend has been that physicians, scientists, government policy advisors, and child advocates who publicly state that vaccines do not cause neurologic problems or autism have been harassed, threatened, and vilified, receiving hate mail and occasionally even death threats [92].

Vaccine Brand Name	Manufacturer	Thimerosal Concentration1		Mercury mcg/0.5 ml
Anthrax	BioThrax	BioPort Corp	**0**	**0**
DTaP	Tripedia	sanofi pasteur	*	*
	Infanrix	GlaxoSmithKline	**0**	**0**
	DAPTACEL	sanofi pasteur	**0**	**0**
DTaP-HepB-IPV	Pediarix	GlaxoSmithKline	**0**	**0**
DTaP-IPV-Hib	Pentacel	sanofi pasteur	**0**	0
DTaP-Hib	TriHIBit	sanofi pasteur	*	*
DTwP	All Products		.01%	25
DT	Diphtheria & Tetanus Toxoids Adsorbed USP multi-dose single dose	sanofi pasteur	.01%	25
			*	*
Td	DECAVAC	sanofi pasteur	*	*
	Tetanus and Diphtheria Toxoids Adsorbed	sanofi pasteur	*	*
Tdap	ADACEL	sanofi pasteur	**0**	**0**
	Boostrix	GlaxoSmithKline	**0**	**0**
Tetanus Toxoid	Tetanus Toxoid Adsorbed USP	sanofi pasteur	.01%	25
	Tetanus Toxoid Adsorbed Adult Use		.01%	25
	Booster		.01%	25
Hib	ActHIB	sanofi pasteur	**0**	**0**
	Hiberix	GlaxoSmithKline	**0**	**0**
	HibTITER	Wyeth-Ayerst	**0**	**0**
	PedvaxHIB liquid (2)	Merck	**0**	**0**
Hib/HepB	Comvax (3)	Merck	**0**	**0**
Hepatitis A	Havrix	GlaxoSmithKline	**0**	**0**
	Vaqta adult/pediatric	Merck	**0**	**0**
Hepatitis B	Engerix-B preservative free	GlaxoSmithKline	**0**	**0**
	Recombivax HB preservative free	Merck	**0**	**0**
Hep A-B	Twinrix	GlaxoSmithKline	**0**	**0**
HPV	Cervarix	GlaxoSmithKline	**0**	**0**
	Gardasil	Merck	**0**	**0**
Influenza 2009/10 Formula	Afluria multi-dose single dose	CSL Limited	.01%	24.5
			0	**0**
	Agriflu	Novartis	**0**	**0**
	Fluarix	GlaxoSmithKline		≤1
	FluLaval	GlaxoSmithKline	.01%	25
	FluMist	MedImmune	**0**	**0**
	Fluvirin	Novartis	.01%	24.5
	Fluzone 5 mL vial No Preservative	sanofi pasteur	.01%	25
			0	**0**

Vaccine Brand Name	Manufacturer	Thimerosal Concentration1		Mercury mcg/0.5 ml
Influenza A H1N1 2009	Influenza A (H1N1) 2009 Monovalent Vaccine multi-dose single dose	CSL Limited	.01%	24.5
			0	**0**
	Influenza A (H1N1) 2009 Monovalent Vaccine multi-dose single dose	Novartis	.01%	24.5
				≤1
	Influenza A (H1N1) 2009 Monovalent Vaccine multi-dose single dose	sanofi pasteur	.01%	25
			0	**0**
	Influenza A (H1N1) 2009 Monovalent Vaccine	GlaxoSmith Kline	.01%	25
	Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal	MedImmune	**0**	**0**
IPV Japanese Encephalitis	IPOL Ixiaro commercial | military	sanofi pasteur Intercell Bio	**0**	**0**
	JE-Vax	sanofi pasteur	0.007%	
Meningococcal	Menactra	sanofi pasteur	**0**	**0**
	MENOMUNE-A/C/Y/W-135 multi-dose single dose	sanofi pasteur	.01%	25
			0	**0**
	Menveo	Novartis	**0**	**0**
MMR	M-M-R II	Merck	**0**	**0**
MMR-Varicella	ProQuad	Merck	**0**	**0**
Polio	IPOL	sanofi pasteur	**0**	**0**
Pneumococcal	Prevnar	Wyeth-Ayerst	**0**	**0**
	Pneumovax 23	Merck	**0**	**0**
Rabies	RabAvert	Chiron	**0**	**0**
	IMOVAX	sanofi pasteur	**0**	**0**
Rotavirus	RotaTeq	Merck	**0**	**0**
Typhoid Fever	Typhim Vi	sanofi pasteur	**0**	**0**
	Vivotif	Berna Biotch	**0**	**0**
Varicella Zoster	Varivax	Merck	**0**	**0**
	Zostavax	Merck	**0**	**0**
Yellow Fever	YF-VAX	sanofi pasteur	**0**	**0**

1. A concentration of 1:10,000 is equivalent to a 0.01% concentration. Thimerosal is approximately 50% Hg by weight. A 1:10,000 concentration contains 25 mcg of Hg per 0.5 mL. (2). A previously marketed lyophilized preparation contained 0.005% thimerosal. (3). COMVAX is not approved for use under 6 weeks of age because of decreased response to the Hib component * This product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal; these amounts have no biological effect. JAMA 1999;282(18) and JAMA 2000;283(16).
Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health. Available at www.vaccinesafety.edu. Accessed 4/17/11.

Table 3. Thimerosal Concentration in Licensed Vaccines.

10. If vaccines are not to blame, why are ASDs increasing?

The increase in prevalence of the ASDs may be explained by three reasons as described by Scahill *et al.* [122]. First, in 1994, with the release of the *Diagnostic and Statistical Manual of Mental Disorders* , 4th edition (*DSM–IV*), there was a broadening of the diagnostic criteria for autism. The *DSM–IV* also added criteria for Asperger's syndrome and clarified the criteria for Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS). Finally, better assessment methods have provided clarification across PDD diagnoses and improved the demarcation between PDD and non-PDD cases. Thus, more recent studies have overcome the systematic undercount of PDD cases in previous studies. The perceived increase in ASDs is therefore likely driven by broadened diagnostic criteria and increased awareness.

11. Role of multiple vaccines and emergence of alternative schedules

With the revelations of the likely fraudulent claims about the MMR vaccine causing ASDs and well-designed studies of thimerosal-containing vaccines failing to show an association with autism, alternative theories about the role of vaccines in causing ASDs have been proposed. The most prominent among these is that the simultaneous administration of multiple vaccines "overwhelms" or "weakens" the immature immune system in young children and through some interaction with the nervous system "triggers" autism in a susceptible host. Sensationalized cases in the media have given credence to this theory. The case that has garnered the most attention is that of a 9-year-old girl with a mitochondrial enzyme deficiency whose encephalopathy, which included features of ASD, was judged to have worsened following the receipt of multiple vaccines at age 19 months [123]. Her family was able to successfully obtain compensation through the US Vaccine Injury Compensation Program (VICP) which was developed in the 1980s to fairly compensate individuals who feel they have been harmed by a vaccine. In the wake of this case, despite reassurances by the CDC that the VICP's action should not be interpreted as scientific evidence that vaccines cause autism, the theory that multiple vaccines given simultaneously can trigger autism has gained credence among the lay press and public.

The idea that multiple vaccines given to young children might either overwhelm an immature immune system or generate a pathologic, autism-inducing autoimmune response is flawed for several reasons. Although the infant immune system is relatively naive, it is capable of generating a vast array of protective responses, starting at birth. In fact, vaccines represent a small fraction of the challenges to a young child's immune system. For example, the average child is infected with 4-6 viruses per year [124], exposing its immune system to numbers of antigens that far exceed those present in simultaneously administered childhood vaccines. Proponents of the theory point to the increasing number of vaccines that are administered to young children. However, most people do not recognize that although the number of recommended childhood vaccines has increased during the past 30 years, with advanced technologies that are used to manufacture modern vaccines, the immunologic load has actually decreased. The childhood vaccines given today contain <200 bacterial and viral antigens, compared with >3000 of these immunological components in the vaccines administered to children in 1980 [125]. In fact, combinations of vaccines are actually known to induce immune responses that are comparable to those given individually [126].

Susceptibility to non-vaccine-preventable infections does not differ in vaccinated and unvaccinated children [127–129]. Put in another way, vaccination does not appear to

suppress the immune system in young children in a clinically relevant manner. On the contrary, infections with some vaccine-preventable diseases are known to predispose children to severe, invasive infections with other pathogens [130,131]. Therefore, the available data suggest that vaccines do not "weaken" the immune system. Furthermore, it should be recognized that autism is not an immune-mediated disease such as multiple sclerosis. There is no evidence of immune activation or inflammatory lesions in the brains of autistic people [116]. Instead, new research suggests that genetic variation in neuronal circuitry that affects synaptic development in the brain might in part account for the symptoms of autism [132]. Therefore, the theory that an exaggerated or inappropriate immune response to vaccination results in autism is at variance with current scientific data that address the pathogenesis of autism.

In 2007, Dr. Robert Sears, a pediatrician from Southern California published *The Vaccine Book: Making the Right Decision for Your Child* [133]. In it he offers 2 alternative schedules (that are not approved or endorsed by any public health authority or professional physician group) to parents who are concerned about vaccines so that they may delay, withhold, separate, or space out vaccines for their children. Dr. Sears has publicly stated that he isn't against vaccinations [134]. Instead, his book suggests an untraditional "alternative" schedule that delays vaccines or spaces them further apart. If parents are unwilling to vaccinate at all, he offers a separate "selective" schedule to encourage them to give their child(ren) at least the "bare minimum" of vaccinations. Healthcare providers are facing many parents who are questioning the need for immunization and insisting that their children receive vaccines according to Dr. Sears' schedule, rather than that recommended by the CDC, the American Academy of Pediatrics, and the American Academy of Family Physicians. Most parents are unaware that no research studies have compared the incidence of autism in vaccinated, unvaccinated, or alternatively vaccinated children (i.e., schedules that spread out vaccines, avoid combination vaccines, or include only select vaccines) [135]. The problem with Dr. Sears' schedules is the fact that it can take up to 5-6 years for children to complete their immunizations, during which some children will be at risk for contracting vaccine-preventable diseases due to lack of adequate immunity. Dr. Sears' book has been described as dangerous by some, because it validates the pervasive myths that are currently scaring parents into making ill-informed decisions for their children [136].

12. Legal repercussions

Perhaps inevitably in a litiginous society, the question of whether childhood vaccines cause autism has moved from the scientific into the legal realm [137-139]. Parents of children with autism have submitted thousands of claims to the federal VICP, seeking damages because they believe that their child's autism was caused by vaccines. In 2002, to resolve such claims more expeditiously, the VICP announced that some "test cases" would examine the general causation question, putting aside the question of harm to any particular child. On February 12, 2009, the U.S. Court of Federal Claims published decisions about these claims, which were considered as a group under the Omnibus Autism Proceeding. The Court, after reviewing 5,000 pages of transcripts, 939 medical articles, 50 expert reports, and hearing testimony from 28 experts, found that the MMR and thimerosal-containing vaccines, independently or together, were not causal factors in the development of autism or ASD [48, 50, 140]. Finally, in *Bruesewitz v. Wyeth* (No. 09-152), the Supreme Court of the United States has held that the National Childhood Vaccine Injury Act "preempts all design-defect claims

against vaccine manufacturers brought by plaintiffs who seek compensation for injury or death caused by vaccine side effects" [141]. In so doing, it likely closed the door on thousands of claims by parents alleging a link between vaccines and childhood autism.

13. Role of the media

As described above, many parents are hesitant about vaccinating their children. Vaccine hesitancy can be explained in part by a lack of trust in those who make vaccine recommendations; a suspicion of profit motive driven by pharmaceutical companies; misinformation on the Internet; failure to appreciate the seriousness of vaccine-preventable diseases, given their low rates; and constant stories in the media claiming that vaccines cause a variety of illnesses, ranging from allergies to autism [135]. In spite of overwhelming scientific evidence to the contrary, the debate over vaccines and ASDs rages on, with media reports fueling the general public's fear. The disconnect between the scientific community and the popular media is clear in a study published by researchers at the Stanford University School of Medicine [142]. They found that while 41 percent of research funding and published scientific papers on autism dealt with brain and behavior research, only 11 percent of newspaper stories in the United States, United Kingdom and Canada dealt with those issues. Instead, 48 percent of the media coverage dealt with environmental causes of autism, particularly the childhood MMR vaccine [142]. However, in a study by Smith *et al*., there was a significant increase in selective MMR non-receipt in the US that was temporally associated with the publication of the original scientific literature suggesting a link between MMR and autism. This decline in MMR vaccination preceded media coverage of the MMR-autism controversy and suggests a limited influence of mainstream media on MMR immunization in the United States [20].

Poland and Jacobson note that there has been opposition to vaccination published in newspapers since the introduction of the first vaccine for smallpox over 200 years ago [143]. According to them, little has changed since that time, although now the antivaccinationists' media of choice are typically television and the Internet, including its social media outlets, which are used to sway public opinion and distract attention from scientific evidence [143]. The authors propose various remedies to the misinformation about vaccines that may be presented in the media. Chief among these is enhanced public education and public persuasion, with increasing scientific literacy at all levels of education. They also recommend public-private partnerships of scientists and physicians be developed to make accurate vaccine information accessible to the public in multiple languages, on a range of reading levels, and through various media outlets.

14. Conclusions

Due to the vaccine discoveries of the 20th century and implementation of successful immunization programs around the world, many infectious diseases such as smallpox, polio and measles have either been eradicated or become rare. Parents and many health care providers of the 21st century have limited or no experience with the devastating effects of these diseases. In parallel, over the last few decades there has been an alarming increase in the number of children diagnosed with autism spectrum disorders (ASDs). Why this increase has occurred is not entirely known, although some explanations have been offered by the medical and scientific community. ASDs are often diagnosed in children at about the

same chronologic age as the peak time for vaccine delivery. This congruence in time of two separate but important health issues, has led to the peculiar situation where fear of disease has shifted to concerns about vaccine safety, particularly ASDs among some members of the public. Although scientific evidence has refuted many of the misconceptions regarding vaccines and ASDs, this information has not been disseminated sufficiently among the lay public. The unfortunate result has been an erosion of public confidence in vaccines. Consequently, some vaccine-preventable diseases such as measles and polio have reappeared in parts of the world where they had been nearly eliminated. In order to restore the public's trust, all stakeholders including parents, healthcare providers and public health authorities need to ensure that rigorously researched scientific information on the issue of vaccines and autism be accurately collected and disseminated.

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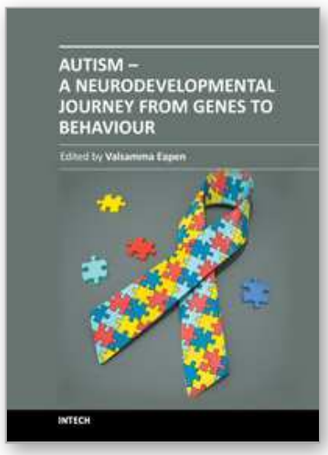
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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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