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# The MMR Vaccine and Autism

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## Abstract

Autism is a developmental disability that can cause significant social, communication, and behavioral challenges. A report published in 1998, but subsequently retracted by the journal, suggested that measles, mumps, and rubella (MMR) vaccine causes autism. However, autism is a neurodevelopmental condition that has a strong genetic component with genesis before one year of age, when MMR vaccine is typically administered. Several epidemiologic studies have not found an association between MMR vaccination and autism, including a study that found that MMR vaccine was not associated with an increased risk of autism even among high-risk children whose older siblings had autism. Despite strong evidence of its safety, some parents are still hesitant to accept MMR vaccination of their children. Decreasing acceptance of MMR vaccination has led to outbreaks or resurgence of measles. Health-care providers have a vital role in maintaining confidence in vaccination and preventing suffering, disability, and death from measles and other vaccine-preventable diseases.

### Keywords

measles; mumps; rubella vaccine; MMR vaccine; autism; autism spectrum disorder; ADS; vaccination; immunization; vaccine safety

## 1. INTRODUCTION AND BACKGROUND

The most damaging vaccine safety controversy of recent years began as an exploration of the possible role of measles and measles vaccines in the pathogenesis of inflammatory bowel disease (IBD). That work eventually evolved into a speculative hypothesis that the combined measles, mumps, and rubella (MMR) vaccine may be a cause of autism. Although numerous scientific studies have refuted a connection between MMR vaccine and autism, some parents are still hesitant to accept MMR vaccination of their children because they are uncertain about the safety of the vaccine. In this review, we summarize the genesis of the controversy, review the scientific evidence against a causal association, describe the effect of the controversy on MMR vaccine acceptance and resurgence of measles outbreaks, and discuss

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The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of any product trade names is for identification purposes only.

what can be done to bolster vaccine confidence, including the central role of scientists and health-care providers.

### 1.1. Autism

Autism, or autism spectrum disorder (ASD) as it is currently defined, is a developmental disability that can cause significant social, communication, and behavioral challenges. A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder (PDD) not otherwise specified, and Asperger syndrome. ASD with regression represents a subset of children with ASD who have lost previously acquired developmental skills, usually language. The causes of ASD are not known, although genetics plays a strong role (1). ASD develops before birth or early in life, and parents of children with ASD usually notice a developmental problem before their child's first birthday (2). The prevalence of ASD has increased in recent years and is estimated to affect 1 in 59 children in the United States (3).

### 1.2. Measles, Mumps, and Rubella

Measles is a highly contagious, acute viral infectious disease caused by a paramyxovirus of the genus *Morbillivirus* and spread by the respiratory route (4, 5). The disease is characterized by a prodrome starting about 10–12 days after exposure consisting of fever (often high) and malaise followed by cough, coryza, and conjunctivitis. The characteristic measles rash, generally occurring around 14 days after exposure, starts as a maculopapular eruption on the head and spreads to the trunk and extremities over the course of 3–4 days (Figure 1a). The rash usually lasts 5–6 days and resolves in the same order in which it appeared. Individuals are infectious from about 4 days before the rash onset to 4 days after the rash onset. Koplik spots, which are blue-white plaques on the mucous membranes of the mouth, are pathognomonic for measles (Figure 1b). Complications of measles include diarrhea, otitis media, pneumonia (viral or bacterial), vision loss, acute encephalitis, seizures, and death. Infection with measles and subsequent recovery confers lifelong immunity (4, 5). Measles remains a significant cause of death and disability in low-income countries (6).

Mumps is an acute viral illness caused by a paramyxovirus of the genus *Rubulavirus* and spread by the respiratory route (7, 8). In young children, mumps tends to be a mild illness with nonspecific symptoms occurring about 12–25 days after exposure. The characteristic parotitis (when it does occur) develops around 16–18 days after exposure. Up to a quarter of those infected with mumps virus are asymptomatic. Orchitis, or inflammation of the testes, is more common in postpubertal males, occurring in 12% to 66% of these individuals. Other complications of mumps, which include aseptic meningitis, encephalitis, pancreatitis, and deafness, are relatively rare but occur more commonly in older children and adults. Infection with mumps virus generally confers lifelong immunity (7, 8).

Rubella, commonly known as German measles, is also an acute viral illness that is spread by the respiratory route (9, 10). It is caused by a togavirus of the genus *Rubivirus*. Signs and symptoms of rubella, which occur about 14 days after exposure, are generally mild and include fever, malaise, upper respiratory symptoms, and a maculopapular rash. Subclinical

infection occurs in up to half of all those infected and is especially common in young children. Complications of rubella are uncommon and occur more often in older children and adults. The main concern with rubella is infection during pregnancy and the subsequent risk of congenital rubella syndrome (CRS). CRS can affect all organ systems in the developing fetus and is more severe when infection occurs early in pregnancy. Fetal demise, premature delivery, deafness, blindness, other severe birth defects, and intellectual disability are some of the health problems associated with CRS, which can be delayed in onset and progress as affected children age. Infection with rubella virus generally confers lifelong immunity (9, 10).

### 1.3. MMR Vaccine

MMR vaccine is part of the recommended US childhood immunization schedule, which is available online from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/vaccines/schedules/index.html). It is recommended as a two-dose series with the first dose at 12–15 months of age and the second dose at 4–6 years of age. Combination MMR vaccines are live virus vaccines indicated for prevention of measles (rubeola), mumps, and rubella. MMR vaccines contain attenuated strains of these three viruses, and various forms of the vaccine have been available since the 1970s (5). MMR vaccine is highly efficacious against measles and rubella, with vaccine effectiveness of around 97% or higher following two doses (4, 9). The two-dose vaccine effectiveness (with Jeryl Lynn strain vaccines) against mumps is lower, around 88% (8). Waning immunity to the mumps component of MMR vaccine has been observed and likely contributes to mumps outbreaks in some types of highly vaccinated populations, such as college students living in dorm settings, necessitating a third MMR dose to help contain outbreaks (11). The combination trivalent MMR vaccine has been the predominant measles-containing vaccine in the United States and other high-income countries for decades. In the United States, MMR and combination measles, mumps, rubella, and varicella (MMRV) vaccines are the only measles-containing vaccines available (4). MMR vaccine has advantages over monovalent vaccines for measles, mumps, and rubella or bivalent measles and rubella vaccines. MMR vaccine requires fewer injections (two shots for two doses of each antigen versus four to six separate shots with bivalent or monovalent vaccines) and reduces the chance for delays in protection that can result from spacing out vaccines over time.

MMR vaccine is well tolerated. Common adverse reactions include injection site reactions, fever (5–15%), and mild rash (5%). MMR vaccine is associated with febrile seizures, which occur at a rate of about 1 in 3,000–4,000 vaccinated children with the first dose. Thrombocytopenia, or low platelet count, is a rare adverse reaction that occurs at a rate of about 1 case per 30,000–40,000 doses. Arthralgia following MMR vaccination has been observed but primarily in adult women (4, 12).

### 1.4. Impact of MMR Vaccination

Live attenuated measles vaccines became available from the early to mid-1960s (5). Their introduction in the United States coincided with a dramatic decline in measles cases by the end of the decade (Figure 2). Combination vaccines that contained live attenuated MMR viruses (MMR vaccine) became available in the United States in 1971 (5). Although there

was a resurgence of measles in 1989–1991 in the United States and elsewhere (13), cases continued to decline, and, in 2000, measles was declared eliminated from the United States (14) (Figure 2), meaning that the disease is no longer continuously transmitted. When measles cases occur in the United States, it is because they are brought in (i.e., imported) from other countries still experiencing measles. Measles was declared eliminated from the Americas in 2016 (15). Global measles vaccination, in the form of MMR vaccine or combination measles-rubella vaccination (used mainly in low-income countries), has resulted in substantial reduction of measles cases and measles deaths (16), a testament to the success of measles vaccination programs worldwide.

Mumps cases also have declined substantially since the introduction of MMR vaccine, although mumps outbreaks continue to occur in the United States, mostly in older children and college-age individuals, even in situations with highly vaccinated populations (11). Likewise, rubella and CRS cases have declined dramatically in the United States since the introduction of MMR vaccine; rubella and CRS were declared eliminated from the United States in 2004 (14) and from the Americas in 2015 (17).

## 2. MMR VACCINE AND INFLAMMATORY BOWEL DISEASE

The possibility that MMR vaccine may cause autism was first raised by Andrew Wakefield and colleagues in 1998. Wakefield had earlier conducted studies of the possible role of measles in IBD, and it was this work in bowel disease that led to a hypothesis about how MMR vaccine could cause a gut pathology that could predispose children to central nervous system toxicity and possibly autism. Although the hypothesis rested on an MMR vaccine–induced bowel disorder, a possible link between the vaccine and bowel pathology was never established and ultimately disproved.

Wakefield's initial study suggesting a possible link between measles vaccine and IBD was an epidemiologic investigation that suggested that measles-containing vaccines increased the risk of Crohn disease and ulcerative colitis (18). However, a subsequent study by some of the same authors did not find an association between measles vaccination and IBD (19). Other studies also did not find evidence that measles-containing vaccines are associated with an increased risk of IBD (20–23). However, these studies involved a monovalent measles vaccine, and Wakefield would later argue that it is the combination MMR vaccine that is the real culprit in enabling the measles vaccine virus to infect the bowel and cause pathology. The most comprehensive study of a possible association between measles vaccines, including MMR vaccine, and IBD was a population-based study conducted in four large health-care organizations in the United States (24). The study subjects were born between 1959 and 1989, with follow-up as long as 25 years or more. The study identified 155 cases of IBD, and each was matched to up to five controls. No increased risk was found for Crohn disease, ulcerative colitis, or any IBD following MMR vaccine specifically or any measles-containing vaccine in general.

Laboratory studies also played into the debate about possible gastrointestinal pathology related to the measles virus or vaccines. Again, one of these was a study by Wakefield that reported finding measles virus nucleocapsid protein in 13 of 15 patients with Crohn disease

(25). However, he and other investigators were unable to replicate these initial findings (26–28).

## 3. AUTISTIC ENTEROCOLITIS

Wakefield's research on measles virus and IBD evolved into a hypothesis that measles vaccination, specifically with MMR vaccine, could lead to a new syndrome of gastrointestinal pathology and neurodevelopmental regression. Wakefield first proposed this idea in a report in *The Lancet* in 1998 (29). The article was a descriptive report of the clinical features of 12 children who had a history of pervasive developmental disorder (nine had autism) and intestinal abnormalities. The only suggested link with MMR vaccination was that for eight of the children, a parent or physician reported worsening of the child's behavioral problems shortly after receipt of MMR vaccine. Despite the limitations of the article (30), it generated intense media and public attention resulting in decreased MMR vaccination coverage, particularly in the United Kingdom, with resultant re-emergence of measles disease and deaths. Although the article was retracted by the journal because of improprieties in subject recruitment and financial conflicts of interest (31–33), the doubts it raised have lingered.

Wakefield has continued to develop and promote his hypothesis. He has claimed that the combination of developmental regression and gastrointestinal disorders following MMR vaccination is a new syndrome that he has called autistic enterocolitis (34). Studies that have attempted to evaluate the emergence of a new syndrome consistent with autistic enterocolitis, including developmental regression and gastrointestinal disorders, have not found links with MMR vaccination. An analysis using a large database of general medical practices in the United Kingdom found that children with autism were no more likely than children without autism to have gastrointestinal disorders requiring medical evaluation before their diagnosis of autism (35). One of the original authors of the autistic enterocolitis hypothesis subsequently reported seeing similar intestinal changes in children without developmental regression and in unvaccinated children (36). Two separate studies found that the proportion of autistic children with regression or with bowel symptoms was not different between time periods before and after the introduction of MMR vaccine (37, 38).

A study that detected persistent measles virus infection in the intestines of children with autism and bowel problems (39) also was promoted to support the autistic enterocolitis hypothesis. The study found that 75 of 91 children with developmental disorders and ileal lymphonodular hyperplasia and enterocolitis had evidence of persistent infection compared with 5 of 70 controls. Limitations of the study included uncertainty about the specific developmental disorders of the study participants (e.g., the proportion with autism) and unknown temporal relationships between measles virus infection and onset of gastrointestinal and developmental disorders. Furthermore, the study did not distinguish whether the virus particles were from vaccine or wild-type measles viruses. A replication study that attempted to overcome the limitations of the preceding study provided strong evidence that autism is not associated with persistent measles virus RNA in the gastrointestinal tract or with MMR vaccine exposure (40). The study examined ileal and cecal tissue specimens from 25 children with autism and gastrointestinal disturbances and 13

children with gastrointestinal disturbances alone using real-time reverse transcription-polymerase chain reaction to detect measles virus RNA. Assays were conducted in three laboratories blinded to diagnosis, including the laboratory that made the original findings of a possible link between measles virus and ASD. All three laboratories found no differences between the two groups in the presence of measles virus RNA in the bowel biopsy samples.

## 4. EPIDEMIOLOGIC STUDIES OF MMR VACCINE AND AUTISM

Beginning soon after publication of the Wakefield paper in 1998, several epidemiologic studies were conducted to evaluate the suggested association between MMR vaccine and autism. The studies used different designs and were conducted in different populations; each found no increased risk of autism following MMR vaccination. The first studies to be reported were ecologic studies in which population-level trends in MMR vaccination were compared with trends in autism (Table 1). The first study was conducted in a district of London and published in 1999 in *The Lancet* (41). This study included an analysis of whether the introduction of MMR vaccine in the United Kingdom in 1988 influenced the incidence of autism. The study found no sudden change in the incidence of autism after introduction of MMR vaccine and no association between receipt of the vaccine and development of autism. In addition, at two years of age, the MMR vaccination coverage among the autism cases was nearly identical to coverage in children in the same birth cohorts in the whole district of London. Other ecological studies comparing trends in measles vaccination coverage with corresponding trends in autism were conducted in the United Kingdom, the United States, Japan, and Canada (42–45). None of these studies found a correlation between increasing trends in autism and measles vaccination coverage (Table 1). However, ecological studies are limited by their reliance on population-level data in which trends in a certain condition could be affected by changes in several other factors in addition to the exposure of interest.

The association between measles vaccination and autism has been evaluated in other studies that used stronger epidemiologic designs, including case-control and cohort studies, that obtain individual-level data and are able to control for confounding factors that could bias the results. Case-control studies assessed the association between measles vaccination and autism by comparing the measles vaccination histories of children with autism with the measles vaccination histories of control children who did not have autism. Case-control studies have been conducted in the United Kingdom, the United States, Poland, and Japan (46–49). None of these studies found an increased risk of autism following measles vaccination with either MMR vaccine or monovalent measles vaccine (Table 1). The largest of the case-control studies, which included 1,294 cases of pervasive developmental disorder and 4,469 controls from the UK General Practice Research Database, found a relative risk of 0.86 [95% confidence interval (CI): 0.68–1.09] for the association between MMR vaccine and pervasive developmental disorder (46), and no increased risk was found for autism specifically.

Two cohort studies have been conducted of MMR vaccination and autism. In the cohort studies, populations of children were identified from birth or early childhood and grouped according to whether they had received MMR vaccine. Computerized record systems were

used to determine which children were subsequently diagnosed with autism, and the rates of autism were compared between vaccinated and unvaccinated children. One of the cohort studies was conducted in Denmark. Using national population and health-care registries, the authors of a retrospective review of all children (>500,000) born in Denmark between 1991 and 1998, including nearly 100,000 who had not been vaccinated with MMR, found no association between MMR vaccination and the development of autism or ASDs (50). The relative risk associated with MMR was 0.92 (95% CI: 0.68–1.24) for autistic disorder and 0.83 (95% CI: 0.65–1.07) for other ASDs. A more recent study addressed the possibility that MMR vaccination is a risk factor only in certain high-risk children (51). The study included about 100,000 younger siblings of children who had been diagnosed with ASD. The study found that receipt of MMR vaccine was not associated with increased risk of ASD even among the higher risk children whose older siblings had ASD.

A meta-analysis of the published epidemiologic studies concluded that MMR vaccine is not associated with an increased risk of autism (52). The evidence for a possible association between MMR vaccine and autism also has been extensively reviewed by three committees of the National Academy of Medicine (53–55), and all have concluded that MMR vaccine does not cause autism.

## 5. IMPACT OF THE MMR VACCINE AND AUTISM CONTROVERSY

In the United Kingdom, the 1998 Wakefield article had a profound impact, with subsequent decreases in MMR vaccination coverage and a dramatic increase in measles cases (56–58). Public confidence in the safety of MMR vaccine showed substantial declines in the early 2000s, possibly influenced by increasing negative media coverage of the MMR vaccine–autism controversy (58). MMR vaccination coverage, which had consistently been above 90% for the first dose in young children in the mid-1990s, sharply declined, dropping to just below 80% by the mid-2000s (58). At the same time, annual measles cases increased from <100 in the late 1990s to a peak of just over 2,000 in 2012 (59). With the retraction of the Wakefield article in 2010 (31) and the accumulating evidence that MMR vaccine does not cause autism, MMR vaccine acceptance and vaccination coverage recovered and stabilized in the United Kingdom (60). By 2010–2011, first-dose MMR vaccination coverage by age 24 months climbed to above 90% and has stayed at >90% through 2017, although coverage has fallen slightly in recent years. Measles case counts have decreased, and, in 2016, measles was declared eliminated from the United Kingdom (61).

The United States also experienced increased antivaccine sentiment and vaccine hesitancy following the publication of the Wakefield article on the alleged MMR vaccine–autism association, but the effect on coverage appeared less obvious than in the United Kingdom, at least at the national level. First-dose MMR vaccination coverage in children 19–35 months old remained ≥90% throughout the 2000s and up to the present (62). However, substantial numbers of parents (up to one-quarter or more) express vaccine hesitancy, with intention to delay or space out vaccinations or not vaccinate at all, or express concerns about the risks and benefits of MMR vaccination and childhood immunizations in general (63, 64). Parents of young children—those with children in the age range for routine MMR vaccination—express the strongest concerns (64). While national coverage with MMR vaccination

remains high, vaccine hesitancy tends to cluster geographically, leaving selected communities vulnerable to introduction and spread of vaccine-preventable diseases (63, 65, 66). In the early to mid-2000s, measles cases in the United States reached record lows with <100 annual cases during most years of the first decade of the twenty-first century (67). However, in the second decade (2011 to 2018), measles outbreaks appeared to be increasing in frequency, resulting in increased case counts (67). Several large outbreaks pushed up case counts in 2013–2015, with 667 cases in 2014 alone (68). These outbreaks originated from imported cases, and most people who developed measles were unvaccinated or had unknown MMR vaccination status (68–71). Fortunately, high levels of MMR vaccination coverage in the population and corresponding population immunity along with targeted isolation and vaccination efforts have contained and controlled these outbreaks. Nevertheless, the threat of continued sporadic outbreaks from imported cases in the United States and in other countries where measles has been eliminated underscores the importance of maintaining a high level of MMR vaccination coverage.

## 6. WHAT CAN BE DONE TO MAINTAIN CONFIDENCE IN VACCINES AND VACCINE COVERAGE?

### 6.1. Robust Postlicensure Vaccine Safety Monitoring Systems and Research Programs

Public confidence in vaccines is boosted by the existence of comprehensive and robust systems to evaluate the safety of vaccines and rapidly detect potential safety problems. The foundation of vaccine safety rests on evaluations that are conducted before a vaccine is ever licensed. Vaccines are extensively tested for safety and efficacy before licensure. Prelicensure clinical trials are effective at identifying and characterizing the most common adverse reactions (72). However, such trials are often not large enough to detect and characterize rare adverse events (73). Furthermore, the generalizability of safety results from clinical trials can be constrained by exclusion criteria that often omit individuals with chronic medical conditions.

Robust postlicensure safety monitoring and research is required to detect and assess new or unexpected safety concerns after vaccines have been licensed (73). These monitoring and research activities provide important data to regulators and public health officials to guide development and implementation of vaccination policies, to reassure health-care professionals and the public on the safety of vaccines, and to take action if vaccine safety problems are detected and confirmed (74).

Vaccine safety monitoring primarily involves spontaneous reporting systems and active surveillance. In spontaneous reporting systems, reports of adverse events following immunization are voluntarily submitted to regulatory or public health authorities or to vaccine manufacturers. Most countries have a spontaneous reporting system, which may be specific for vaccines or used for both vaccines and drugs. The United States has a jointly managed CDC and US Food and Drug Administration (FDA) program called the Vaccine Adverse Event Reporting System (75). Spontaneous reporting systems are intended for early detection of possible vaccine safety problems and are not designed to assess causality. Safety

signals (76) detected in spontaneous reporting systems often need to be assessed further in more robust data systems.

Active surveillance for vaccine safety in the United States relies on near real-time sequential monitoring of vaccine safety using large-linked electronic health record databases that have information on vaccinations, medical encounters, and demographics for a covered population (77). Because population-based information (numerator and denominator) is available in active surveillance systems, it is possible to estimate the risk of adverse events. In the United States, the CDC conducts active surveillance through its Vaccine Safety Datalink project (78), and the FDA uses the Post-Licensure Rapid Immunization Safety Monitoring program (79).

Comprehensive vaccine safety monitoring and research programs are essential to providing timely safety data, but just as important is the forum through which the information is communicated. National advisory committees, such as the CDC's Advisory Committee on Immunization Practices (ACIP), are composed of individuals outside of government and convene regularly at public meetings to hear and discuss data on vaccine safety, effectiveness, and benefit-risk balance (74). The open and transparent deliberation process of the ACIP, which includes input from the public in the form of spoken or written comments, can enhance the credibility of vaccination policy recommendations and increase confidence in public health organizations advocating for vaccination programs.

### 6.2. Communication and the Role of the Health-Care Provider

Scientific data are essential in the monitoring and evaluation of vaccine safety, but scientific evidence alone often is not sufficient to provide reassurance about vaccine safety. Although most parents support immunizations, many have concerns or misconceptions that could erode their confidence in vaccines (80–83). Fortunately, immunization coverage in US children is high. Nonetheless, a sizable fraction of parents do not have their children fully immunized, and concern about vaccine safety is a leading reason for underimmunization. These concerns persist despite the scientific evidence that vaccines do not cause autism or a host of other conditions that have been alleged to be caused by vaccines. It is therefore critically important that public health agencies, medical organizations, and other influential authorities continue to focus on the safety of vaccines and assure public confidence by (*a*) providing clear, consistent messages about vaccine safety concerns; (*b*) supporting effective and transparent vaccine safety monitoring systems and research activities; (*c*) providing reviews and recommendations by respected independent expert groups on vaccine safety controversies; and (*d*) engaging advocacy groups in constructive and open dialogue about their vaccine safety concerns.

Parents regard primary health-care providers as their most trusted source for information on immunizations (80, 84, 85). Thus, health-care providers who administer vaccines must be able to effectively communicate the benefits and risks of vaccines. Such communication includes listening with empathy and addressing concerns of parents and patients with honest and direct information to allows informed decisions to be made. The American Academy of Pediatrics does not advise pediatricians to remove nonvaccinating families from their practices. Instead, pediatricians should listen carefully and respectfully to parents'

immunization concerns, factually communicate the benefits and risks of vaccines, and work with parents who may be concerned about having their child vaccinated (86). In the United States, Vaccine Information Statements (VISs) are the cornerstone of provider-patient vaccine benefit-risk communication. VISs are required to be provided to a patient or a patient's parent or legal representative (in the case of a child) before every dose of vaccines that are covered under the National Childhood Vaccine Injury Act of 1986. In practice, the CDC makes VISs available for nearly all US-licensed vaccines regardless of covered status. An increasing number of resources that address vaccine safety concerns, including misconceptions and unsubstantiated allegations, are available, including websites, brochures, resource kits, and videos. More information on vaccine risk communication resources can be obtained at http://www.cdc.gov.

### 6.3. School Attendance Requirements and Stricter Vaccine Exemptions

Vaccination requirements for attendance at childcare facilities and schools are tools to incentivize parents to vaccinate children with MMR and other routinely recommended childhood immunizations (87). However, these types of requirements, or mandates, and the inevitable objections to them underscore the tension between societal interests and individual interests in matters of public health (88). The rationale for school vaccination mandates is that the interests of the group—members of a classroom, a school, a school system, and those who have contact with schoolchildren—take precedent over the rights of any one individual. Although vaccines are not risk free, the benefits of vaccination in preventing the spread of infectious diseases in a school setting and beyond outweigh the risks of adverse events in an individual child, especially in a situation where that child is benefiting from a common good or community resource, such as a public school.

In the United States, all states have vaccination requirements for attendance at public schools, as do most private schools and childcare facilities. However, the nature and types of vaccination exemptions vary widely, with religious, philosophical, or personal belief exemptions available in most states, and all states allow medical exemptions. Furthermore, requirements for receiving and maintaining medical and nonmedical exemptions also vary (89). Three states—California, Mississippi, and West Virginia—allow only medical exemptions. California's current strict exemption law went into effect in 2015; the following year the state saw a substantial increase in medical exemptions, indicating that parents opposed to vaccination might have searched out physicians willing to provide medical exemptions liberally within the context of the law (90). The availability and ease of obtaining nonmedical exemptions are associated with the likelihood that parents will request such exemptions (91–93). The relationship between the availability and ease (or strictness) of obtaining nonmedical exemptions on early childhood vaccination coverage and the incidence of vaccine-preventable diseases is mixed (91, 94, 95). However, states that allow only medical exemptions have relatively high coverage of required vaccines for enrolled kindergartners (96). Since nonmedical exemptions tend to cluster geographically (65, 66), isolated pockets of low MMR vaccination coverage (and susceptibility to measles spread) can exist in communities despite high overall state and national coverage.

### 6.4. Resurgence of Vaccine-Preventable Diseases

Lack of acceptance of vaccination with consequent decreases in vaccination coverage leads to resurgence of vaccine-preventable diseases, as was demonstrated with pertussis vaccination in several countries in the 1970s and 1980s (97) and MMR vaccination in the United Kingdom and the United States more recently. The resurgence of disease is then followed by increased acceptance of vaccination. It would be tragic if this were to be the path to restoring confidence in MMR vaccination. Everything should be done to avoid a scenario where widespread resurgence of measles, with its attendant suffering, disability, and death, becomes the motivating force for renewed acceptance of MMR vaccination.

## Glossary

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| **IBD** | inflammatory bowel disease |
| **MMR vaccine** | measles, mumps, and rubella vaccine |
| **PDD** | pervasive developmental disorder |
| **ASD** | autism spectrum disorder |
| **CRS** | congenital rubella syndrome |

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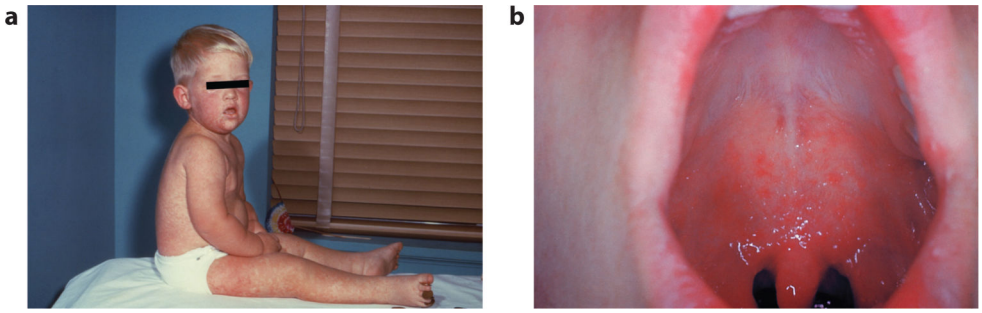


**Figure 1.**

(*a*) Child with characteristic red, blotchy rash on third day of the measles rash. (*b*) Koplik spots on the soft palate and oropharynx due to pre-eruptive measles on day 3 of the illness.

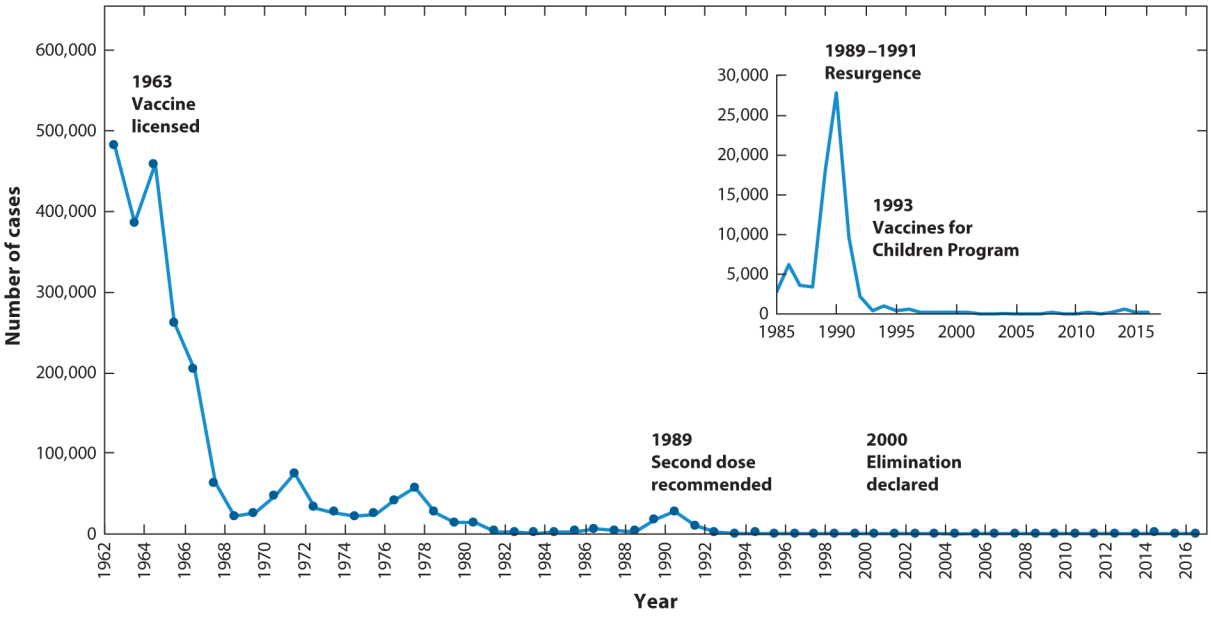


**Figure 2.**

Measles cases in the United States, 1962–2016. Data taken from the National Notifiable Diseases Surveillance System (https://wwwn.cdc.gov/nndss/).

**Table 1**

Epidemiologic studies of MMR vaccines and ASD

| Study | Design | Years | Population | Comparison | Outcome(s) | Finding(s) |
|---|---|---|---|---|---|---|
| 41 | Ecological and case scries | 1979–1998 | Children in eight UK health districts born during 1979–1992, including 498 cases of autism | Trends in incidence before and after introduction of MMR vaccination to the United Kingdom in 1988 | Annual trends in autism<br>Temporal clustering of autism onset or developmental regression | No sudden increase in autism cases after introduction of MMR vaccination<br>No temporal clustering after vaccination |
| 43 | Ecological | 1980–1994 birth cohorts | California kindergartners | MMR coverage and autism occurrence | Annual trends in autism cases | No correlation between level MMR coverage and large increase in autism cases |
| 44 | Ecological | 1988–1996 birth cohorts | Yokohama, Japan, children up to age 7 years | ASD incidence before and after termination of MMR vaccination program | Annual trends in ASD incidence | ASD incidence continued to increase after withdrawal of MMR vaccination |
| 42 | Ecological | 1988–1999 | UK general practice patients 12 years and younger, with a focus on boys 2–5 years of age | Time trend analysis of MMR vaccination coverage and autism incidence | First recorded diagnosis of autism | Autism incidence increased fourfold while MMR vaccination was steady at >95% in boys 2–5 years |
| 45 | Ecological | 1987–1998 birth cohorts | Schoolchildren in Montreal, Canada (*N* = 27,749) | PDD time trends relative to trends in MMR vaccination | PDD(*n* = 180), including autism | PDD rates increased while MMR vaccination coverage decreased |
| 46 | Case control | 1987–2001 | UK general practice patients born in 1973 or later<br>Cases (*n* = 1,294)<br>Controls (*n* = 4,469) | MMR vaccinated versus unvaccinated | First recorded diagnosis of PDD, with subgroup analysis of first diagnosis of autism (*n* = 991) | MMR vaccine was not associated with an increased risk of autism or other PDDs |
| 47 | Case control | 1986–1993 birth years | Atlanta, Georgia, schoolchildren 3–10 years old in 1996<br>Autism cases (*n* = 624)<br>School-matched controls (*n* = 1,824) | Age at first MMR vaccination | Autism and autism subgroups | The distribution of ages at MMR vaccination was similar in the cases and controls |
| 48 | Case control | Not stated (includes years before and after 2004 when MMR was included in the Polish vaccination schedule) | Children 2–15 years old in a region of Poland<br>Autism cases (*n* = 96)<br>Controls (*n* = 192) | Vaccinated versus unvaccinated with MMR or single antigen measles vaccine | Diagnosis of autism First symptoms of autism | No increased risk of autism found in any of the comparisons including after single antigen or MMR vaccines” |
| 49 | Case control | 1984–1992 birth years | Yokohama, Japan<br>Cases diagnosed with ASD by 1997<br>ASD cases (*n* = 189)<br>Matched controls (*n* = 224) | MMR vaccination | ASD | No increased risk of ASD associated with MMR vaccination |
| 50 | Retrospective cohort | 1991–1998 birth cohorts | Children in Denmark (*N* = 537,303) | Vaccinated versus unvaccinated | Autistic disorder (*n* = 316)<br>Other ASD(*n* =422) | Risk of autistic disorder or other ASD was not increased by MMR vaccination |
| 51 | Retrospective cohort | 2001–2012 | Privately insured US children who had older siblings with or without ASD (*N* = 95,727) | ASD diagnosis according to MMR vaccination status and sibling ASD status | ASD diagnosis up to age 5 years (*n* = 994) | MMR not associated with increased risk of ASD, even among high-risk |

| Study | Design | Years | Population | Comparison | Outcome(s) | Finding(s) |
|---|---|---|---|---|---|---|
| | | | | | | infants with an older sibling with ASD |

Abbreviations: ASD, autism spectrum disorder; MMR, measles, mumps, and rubella; PDD, pervasive developmental disorder.