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Review

The relationship between autism and autism spectrum disorders and vaccination: review of the current literature

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ABSTRACT

This study evaluates the alleged relationship between childhood vaccination—specifically the MMR (measles, mumps, rubella) and DPT (diphtheria, pertussis, tetanus) vaccines—and the development of autism spectrum disorders (ASD). It addresses public concerns by reviewing existing literature and highlighting the essential role of vaccines in public health. A comprehensive analysis of scientific studies, including systematic reviews, meta-analyses, and population-based investigations, was conducted, with particular attention to research on temporal associations, thimerosal content, and proposed immunological mechanisms. The findings consistently show no causal link between childhood vaccinations and ASD. Neither the MMR vaccine nor thimerosal-containing vaccines were associated with an increased risk of ASD, as confirmed by large-scale cohort studies and international meta-analyses. Additionally, no evidence supports claims that temporal patterns or atypical forms of ASD are related to vaccination. Overall, the current scientific consensus strongly refutes the notion that vaccines cause autism. The findings support the continuation of current immunization programs, stressing the importance of combating misinformation, reinforcing public trust, and safeguarding community health through sustained vaccination efforts. No changes to existing vaccine protocols are warranted.

Keywords: childhood, vaccines, autism, autism spectrum disorder

INTRODUCTION

In the past few years, the concerns regarding the potential relationship between autism and autism spectrum disorders and vaccination have significantly increased. Especially, vaccines such as MMR (measles, mumps, and rubella) and DPT (diphtheria, pertussis, and tetanus) are the ones that are most blamed.[1] The societal worry that childhood vaccination possibly causes autism, increased the distrust in vaccination, thus leading to the resurgence of illnesses (e.g., rubeola, mumps, measles, etc.) that could be prevented by vaccines.[1]

The importance of vaccines on community health is undeniable. Decisions on withdrawing vaccination because of concerns about autism should be attentively evaluated following current evidence. In the last ten years, there have been several pieces of work examining the connection between autism, ASD, and childhood vaccination, and the discussions around it are still proceeding. The search with the keywords “vaccine” and “autism” gives 67,700 article results on Google Scholar; the majority are about MMR and DPT vaccines. This review aims to address the allegations about the link between autism and vaccines from a scientific point of view and to draw attention to this issue, which is highly crucial for community health.

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Background and significance

Autism and Autism Spectrum Disorder (ASD) are lifelong and severe developmental disorders that are characterized by repetitive, limiting, and inflexible behaviors that cause social, communicational (speaking, language), and behavioral (defined and repetitive) difficulties.[2,3] Autism is at the very severe end of the ASD.[3] Symptoms such as mental retardation, epilepsy, and chronic gastrointestinal disorders are common, along with hyperactivity in some cases.[4] Asperger syndrome, the pervasive developmental disorder not otherwise specified (PDD), and autistic disorders are within the ASD categories.[4]

The frequency of ASD is progressively increasing; while the prevalence of autism in the USA was 1 in 2500 children in the mid-80s, it rose to 1 in 300 in the mid-90s.[5] Another study reported that the prevalence of ASD among children aged 6-11 years increased from 3 per 10,000 in 1991-1992 to 52 per 10,000 in 2001-2002.[6] However, it's still unclear whether this increment is real or due to a rise in awareness.[2] Moreover, it is reported that the impact of some environmental risk factors that have not yet been identified should not be ignored.

Parents of children with ASD often notice developmental difficulties in their children in the first year of life.[4] Many parents blame themselves, thinking that the problem may be caused by risky behavior during pregnancy, advanced gestational age, vaccines administered, or a genetic factor.[4,6] The underlying causes of ASD are multifactorial and have a strong genetic component. In very few cases, a specific cause has been identified. Neurological findings associated with autism probably emerge in the early stages of embryonic development.[2] Communication delays and characteristic findings usually become apparent later in life, often after age three. However, since the neuropathological condition underlying autism is present at birth in the majority of cases, it has been suggested that vaccines administered after birth are unlikely to cause autism.[2] In most cases, no abnormal findings may be observed initially during the child's developmental stages; however, developmental stages may regress during follow-up. Such cases of regressive autism raise the theory of a biological link to vaccination. Despite extensive research on the etiology and pathophysiology of autism, few results have been obtained regarding a basic causal mechanism.[4]

Review of the literature

Many parents are concerned about the safety of vaccines given to their infants and children, especially because of the suggestion that the MMR vaccine may be linked to the development of autism.[2,4] One of the most important findings supporting the hypothesis of a link between MMR and autism is the detection of measles virus nucleic acid sequences in the blood cells and intestines of affected children.[3,4] Other researchers have not been able to detect measles virus genome sequences in the leukocytes of autistic children vaccinated with MMR.[5] Independent researchers have found no evidence of a unique syndrome of gastrointestinal disorders or neurodevelopmental regression in children with autism who received the MMR vaccine. Furthermore, no correlation was found between the timing of vaccination and the onset of neurodevelopmental regression.

In February 1998, British gastroenterologist Dr. Andrew Wakefield published an article in *The Lancet* suggesting a link between the MMR vaccine and the development of autism. This article sparked controversy about the safety of vaccines.[7] Wakefield and colleagues[7] claimed that the MMR vaccine caused intestinal dysfunction (inflammatory bowel disease) and impaired absorption of essential nutrients, leading to neurodevelopmental delay and behavioral disorders in 12 cases. Behavioral disorders included autism (nine cases), disintegrative psychosis (one case), and possible postviral or vaccine-associated encephalitis (two cases).[7] This situation has led to a generally negative attitude of parents towards vaccines in both Europe and the United States.[4] The fact that no details were provided about the source population and no "unaffected" control group in the relevant article has caused the hypothesis to receive much criticism as one of its weakest points. It has been emphasized that the association between vaccines and autism is coincidental and that the vaccine is not a cause.[2] It has been underlined that the most frequently detected intestinal abnormality in these patients was ileocolonic lymphonodular hyperplasia and that this condition may not necessarily represent a pathological condition.[2] Wakefield's group[8-11] reported laboratory evidence of the measles virus genome in peripheral white blood cells and intestinal biopsy samples of several patients with mild intestinal inflammation associated with ileocolonic lymphonodular hyperplasia and behavioral regression.[7,8] However, it is not clear whether these laboratory findings have clinical significance. Later studies by Wakefield et al.[7,12] and other investigators have also not supported this hypothesis.[2,13] There was no evidence of measles virus persistence in the peripheral blood mononuclear cells of children with ASD.[14] Because the supposed link between bowel disease and autism was weak and because bowel disease did not

precede the onset of autism in any of the reported cases, the British Medical Research Council took strong action against Wakefield, and his article, published in *The Lancet*, was retracted 12 years later.[4,7] However, as a result of the anti-vaccine movement that began during this period, measles was declared endemic in England and Wales for the first time after 14 years in 2008. These years were a period when hundreds of thousands of children in England were left unprotected due to anti-vaccine sentiment, and public health units made intensive efforts to increase parental confidence in vaccination.[15]

After Wakefield's article, several epidemiologic studies investigated the possible link between autism and the MMR vaccine, and this hypothesis was rejected.[2,3,13] Regardless of the scientific data, it has been assumed that if the mumps virus is not responsible for autism, another MMR component must be responsible.[4]

Following Wakefield et al.[7], in a systematic meta-analysis[16] which evaluated data from 12 studies and five different countries, various hypotheses regarding the relationship between autism and vaccination were suggested.[2,16] The first hypothesis states that ASD frequency increases in people who received the MMR vaccine compared to those who did not receive the vaccine. In a retrospective cohort study conducted by Madsen et al.[17], no statistically significant difference was found in the rates of autism or ASD between MMR-vaccinated and unvaccinated subjects during the same period. The second hypothesis is that ASD occurs at an increased rate because of MMR vaccination. Regarding this hypothesis, six studies have examined whether there is a relationship between MMR vaccination and changes in ASD rates.[13,18-22] These analyses were conducted in the United Kingdom, Sweden, and the United States. Four of the studies found no significant relationship between MMR vaccination and an increase in ASD or ASD variants.[20-23] One of the other two studies evaluated the increase in ASD cases before and after the MMR vaccination programs were initiated and found no increase in ASD rates during the vaccination period.[18] In a study by Fombonne et al.[13], no significant difference was found in the rates of neurodevelopmental regression in the sample before and after MMR vaccination was introduced (15.6% and 18.4%, respectively), and no evidence was found to support MMR-induced autism or "autistic enterocolitis" syndrome. Based on these findings, the researchers recommended that no changes be made to current vaccination programs or to vaccination recommendations.[13] The third hypothesis is that there is a temporal relationship between the development of ASD and MMR vaccination. Eight studies were evaluated for this purpose.[13,17,22-27] Three of these studies compared the age at which ASD was diagnosed, or parental concern arose, in vaccinated and unvaccinated individuals.[13,17,23] The hypothesis in these studies is that if MMR vaccination causes ASD, the populations exposed to the vaccine should develop ASD at a different age than the unexposed populations. However, these three studies found no difference in the mean age at which ASD was diagnosed. Six other studies examined whether there was an increase in the frequency of ASD diagnosis or evidence of features suggestive of ASD after children were vaccinated with MMR. One of these studies did not show that children diagnosed with autism had more frequent physician visits after MMR vaccination when compared to a non-autistic control group.[26] Another study, and an extended analysis of this study, examined a cohort of children with ASD and found that these children were not more likely to be diagnosed with ASD or to have developmental delays at certain points after receiving MMR vaccination.[23,25] Increased parental concern was observed in the 6-month period following vaccination, but this was not significant at other points after MMR vaccination.[23,25] Another study compared rates of parental concerns about bowel symptoms or neurodevelopmental regression among children with autism who received the MMR vaccine, children who were autistic before the MMR vaccine, and children with autism who were not vaccinated, and found no significant differences.[22] A separate study found no cases of ASD among 1.8 million people who received the MMR vaccine.[24] A study in Finland found no evidence of increased hospitalizations for autism after children were vaccinated with the MMR vaccine.[27] A study in Denmark of a population cohort of MMR vaccinated (400,000 cases) and unvaccinated children (100,000 cases) found no increased risk of developing autism or ASD with MMR vaccination. The relative risk associated with MMR was 0.92 (95% confidence interval (CI): 0.68–1.24) for autistic disorder and 0.83 (95% CI: 0.65–1.07) for other autism spectrum disorders.[17] A large, population-based case-control study conducted by the Centers for Disease Control and Prevention (CDC) also found no evidence to support an association between MMR and autism.[28] The fourth hypothesis is that the MMR vaccine may be associated with a new variant form of ASD. Four studies have examined a specific association of the variant form of ASD with MMR vaccine.[13,22,27,29] Variant ASD was defined by the presence of developmental delay or gastrointestinal symptoms. None of the 31 children who developed Gastrointestinal (GI) symptoms after MMR vaccination (three studies and one case report) developed ASD during clinical follow-up.[29] In another study, when comparing the historical

period after the introduction of the MMR vaccine with the historical sample before the vaccine became routine, no difference was found in the rates of developmental delays in children diagnosed with ASD.[13] Another study found no increase in the percentage of children with autism who had GI symptoms or developmental delay after MMR vaccination.[22] Another study found that none of the 309 children who received MMR vaccination and were subsequently hospitalized for autism were also hospitalized for inflammatory bowel disease.[27]

Taylor et al.[1] evaluated 498 known ASD cases born in a London district in 1979 and later found that although the number of cases had increased since 1979, there was no sharp increase after the introduction of the MMR vaccine in 1988. The study found no temporal relationship between vaccination and the onset of regression. They also found that all children with ASD who were vaccinated with MMR before 18 months of age, after 18 months of age, or not vaccinated with MMR at all had similar ages of diagnosis, and that MMR vaccination did not cause autism to appear at an earlier age.[1]

Studies in Japan and Canada have found no relationship between the MMR vaccine and the prevalence of autism.[30,31] A study conducted in Japan found that the prevalence of autism increased in children born between 1988 and 1996, despite MMR vaccination being completely stopped in 1993, and that there was no difference in terms of the decline in autism rates.[30,31] Similarly, a study conducted in Montreal found that the prevalence of autism and pervasive developmental disorders increased from 1987 to 1998, despite the decline in MMR vaccination.[30]

Although observational studies have not found an increased risk of autism after MMR vaccination, concerns about the putative link between the MMR vaccine and autism persist almost two decades after the controversial and later retracted 1998 Lancet article,[1] making it difficult to accept the vaccine. A 2012 Cochrane review (5 randomized controlled trials, one controlled clinical trial, 27 cohort studies, 17 case-control studies, five time-series studies, one crossover study, two ecological studies, and six self-controlled case series studies) found no qualitative evidence of an association between the MMR vaccine and autism.[32] A 2014 meta-analysis identified 10 observational studies on childhood vaccines, including five cohort and five case-control studies: two cohort studies and four case-control studies specifically cited no association between MMR and autism.[1] Similarly, a recent epidemiological study conducted in the USA in 2001 did not show any association between the MMR vaccine and the risk of inflammatory bowel disease.[19] In another meta-analysis study, Mohammed et al.[4] evaluated the results of 21 systematic studies published between 1998 and 2018 and found no causal relationship between childhood vaccination and the development of autism.

Possible mechanism for developing autism following vaccination

Various mechanisms have been put forward regarding the relationship between vaccination and the development of autism (immune system dysfunction, gliadorphin side effects, mercury toxicity, etc.). According to this mechanism, frequent stimulation of the immune system through vaccination causes changes in immunological function in the developing central nervous system, resulting in a strong microglial reaction and consequently dendritic and synaptic losses. When the microglial system is activated, the immune cells of the brain secrete inflammatory cytokines, free radicals, lipid peroxidation products, and excitotoxins such as glutamate and quinolinic acid. As a result, the clinical and pathological features of autism emerge.[4]

Thimerosal is an organic chemical that contains ethylmercury and has been used as a preservative in vaccines since the 1930s. Thimerosal is 49.6% mercury by weight and is metabolized to ethylmercury and thiosalicylate. Ethylmercuric hydroxide rapidly penetrates the brain and is converted to inorganic mercury.[4] In the late 1990s, partly due to increased awareness of the risks of exposure to low doses of organic mercury, the Food and Drug Administration conducted a risk assessment of the use of thimerosal in vaccines.[2] Between 1989 and 1998, as more vaccines (Hepatitis B, Haemophilus influenzae type B, etc.) were added to the recommended infant vaccination schedule, there was an increased exposure to mercury from vaccines. It has been shown that infants vaccinated according to the recommended schedule may have received mercury doses that exceed the Environmental Protection Agency's methylmercury exposure limit.[33] Biological and epidemiological evidence has shown a direct relationship between increasing mercury doses in thimerosal-containing vaccines and neurodevelopmental disorders. A close correlation between thimerosal and autism has been suggested because of the increasing prevalence of autism observed from the late 1980s to the mid-1990s in association with increasing mercury doses in childhood vaccines containing thimerosal.[34] Geier et al.[34] evaluated the CDC Biological Surveillance Summaries, US Department of Education data sets, and CDC annual live birth estimates,

concluding that the contribution of thimerosal (>50% effect) from childhood vaccines to the observed prevalence of autism was higher than that of the MMR vaccine. As a result of this study, it was recommended that thimerosal be removed from all vaccines and that additional research be conducted to produce an MMR vaccine with a better safety profile.[34] Geier et al.[5] examined the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US Department of Education Report to determine dose-response curves between increasing thimerosal doses in childhood vaccines and neurodevelopmental disorders. It was shown that the increases in neurodevelopmental disorders observed were closely and linearly related to increasing mercury doses from thimerosal-containing childhood vaccines. The authors suggested that the emergence of neurodevelopmental disorders following thimerosal-containing childhood vaccines was not coincidental based on the evidence presented here.[5]

In a population-based cohort study, Hviid et al.[35] found no significant difference in autism and other ASD symptoms and findings when comparing children vaccinated with the same pertussis vaccine with and without thimerosal (relative risk (RR) = 0.85 [95% confidence interval (CI) = 0.60–1.20] for autism; RR = 1.12 [95% CI = 0.88–1.43] for other ASD). Moreover, the lack of evidence of a dose-response correlation was emphasized in the same study (increase in RR per 25 µg ethylmercury = 0.98 [95% CI = 0.90–1.06] for autism and 1.03 [95% CI = 0.98–1.09 for ASD). Consequently, no adverse effects were found in terms of cumulative mercury dose and thimerosal exposure when comparing ASD and ASD developmental disorders.[1] Despite all these positive and negative data, the Public Health Service and the American Academy of Pediatrics called for the removal of thimerosal from infant vaccines as a precautionary measure, despite the lack of any evidence of harm.[2]

CONCLUSION

This review evaluates the relationship between the MMR vaccine and autism and ASD. When epidemiological studies conducted on this subject in the literature are evaluated, no evidence has been found for a link between the MMR vaccine and autism. Although the risk of autism from MMR remains theoretical according to current literature, there are many studies showing the negative effects of not being vaccinated on health. Public health authorities should make efforts to alleviate public concerns about vaccination based on literature data and emphasize the importance of vaccines for public health. When literature data is evaluated, there is no scientific evidence for a vaccine-autism relationship, and therefore no changes are required in current vaccination programs.

Author contribution

Review conception and design: GÖ, EÇ; literature review: EÇ; draft manuscript preparation: EÇ, GÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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