POREMEĆAJ IZ SPEKTRA AUTIZMA I VAKCINACIJA: RAZBIJANJE MITOVA I PREDSTAVLJANJE ČINJENICA

PREGLEDNI RAD

REVIEW ARTICLE

AUTISM SPECTRUM DISORDER AND VACCINATION: DISPELLING MYTHS AND PRESENTING EVIDENCE

Aleksandra Ristić[1], Aleksandra Stojanović[1], Sofija Stevanović[1]

[1] Univerzitetski klinički centar Niš, Centar za zaštitu mentalnog zdravlja, Niš, Srbija

[1] *University Clinical Center Niš, Center for Mental Health Protection, Niš, Serbia*

SAŽETAK

Uvod/Cilj: Poremećaj iz spektra autizma (PAS) predstavlja složen neurorazvojni poremećaj čija etiologija nije u potpunosti razjašnjena. Nakon objavljivanja rada Endrua Vejkfilda 1998. godine, kojim je sugerisana moguća povezanost MMR vakcine i PAS-a, došlo je do značajnog pada poverenja u vakcinaciju i porasta zabrinutosti javnosti. Cilj ovog rada bio je pregled i analiza dostupnih naučnih dokaza o povezanosti MMR vakcine i poremećaja iz spektra autizma.

Metode: Izvršen je pregled dostupne naučne literature koja se odnosi na MMR vakcinu i poremećaj iz spektra autizma, sa posebnim osvrtom na epidemiološke studije, kohortne studije, sistematske preglede i metaanalize koje su ispitivale moguću povezanost između vakcinacije i razvoja PAS-a.

Rezultati: Analizirana istraživanja dosledno pokazuju da ne postoji uzročno-posledična povezanost između primene MMR vakcine i razvoja poremećaja iz spektra autizma. Istovremeno, pad obuhvata vakcinacijom povezan je sa ponovnom pojavom epidemija malih boginja u brojnim zemljama. Savremeni naučni dokazi potvrđuju bezbednost i efikasnost MMR vakcine.

Zaključak: Dostupni naučni dokazi jasno pokazuju da MMR vakcina ne povećava rizik za nastanak poremećaja iz spektra autizma. Kontinuirana edukacija zdravstvenih radnika i roditelja, zasnovana na naučnim dokazima, od ključnog je značaja za suzbijanje dezinformacija, jačanje poverenja u vakcinaciju i održavanje visokog obuhvata imunizacijom.

Ključne reči: MMR vakcina, poremećaj iz spektra autizma, vakcinacija

ABSTRACT

Introduction/Objective: Autism spectrum disorder (ASD) is a complex neurodevelopmental condition with a multifactorial and not yet fully understood etiology. Following the publication of Andrew Wakefield's 1998 paper suggesting a possible association between the measles, mumps and rubella (MMR) vaccine and ASD, public confidence in vaccination declined substantially. This review aimed to examine and summarise the current scientific evidence on the association between MMR vaccination and ASD.

Methods: A narrative review of the available scientific literature was conducted, focusing on epidemiological studies, cohort studies, systematic reviews, and meta-analyses evaluating the potential association between MMR vaccination and ASD.

Results: The reviewed evidence consistently shows no causal association between MMR vaccination and ASD development. Conversely, declining vaccination coverage has contributed to the re-emergence of measles outbreaks in several countries. Current evidence strongly supports the safety, effectiveness, and favourable benefit-risk profile of the MMR vaccine.

Conclusion: Available scientific evidence confirms that the MMR vaccine does not increase the risk of ASD. Promoting evidence-based communication and maintaining high vaccination coverage remain essential to prevent vaccine-preventable diseases and address vaccine hesitancy.

Keywords: MMR vaccine, autism spectrum disorder, vaccination

Autor za korespondenciju:
Aleksandra Ristić
Centar za zaštitu mentalnog zdravlja, Univerzitetski klinički centar Niš
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija
Elektronska adresa: ristic.aleksandra1995@gmail.com

Corresponding author:
Aleksandra Ristić
Center for Mental Health Protection, University Clinical Center Niš
48 Dr Zoran Đinđić Boulevard, 18000 Niš, Serbia
E-mail: ristic.aleksandra1995@gmail.com

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UVOD

Imunizacija predstavlja jedno od najvećih dostignuća medicine i i dalje je najefikasniji način prevencije zaraznih bolesti [1]. Zahvaljujući imunizaciji, milioni dece i odraslih zaštićeni su od teških bolesti i smrtnog ishoda [1]. Međutim, uprkos uspehu imunizacije, sumnje, nepoverenje i strah od neželjenih događaja doprineli su oklevanju u vezi sa vakcinacijom i ponovnoj pojavi bolesti koje se mogu sprečiti vakcinacijom, naročito morbila, u nekoliko zemalja [2].

U pojedinim slučajevima, strah od potencijalnih neželjenih efekata čak je prevazišao strah od komplikacija koje izazivaju same bolesti [3]. Jedan od najuporнijih izvora nepoverenja u vezi sa vakcinacijom bila je kombinovana vakcina protiv morbila, zaušaka i rubeole (MMR) [3]. MMR vakcina, koja štiti od morbila, zaušaka i rubeole, primenjuje se već decenijama [1]. Ovo nepoverenje potiče iz 1998. godine, kada je Andrew Wakefield objavio članak u časopisu *The Lancet*, u kojem je izneo tvrdnju o navodnoj povezanosti između MMR vakcine i pojave poremećaja iz spektra autizma (PSA) [3–5].

Wakefieldov članak, koji je kasnije povučen iz publikacije i čiji rezultati nikada nisu naučno potvrđeni, privukao je značajnu pažnju medija i izazvao strah među roditeljima [3–5]. Od tada su sprovedena brojna epidemiološka istraživanja, od kojih nijedno nije pokazalo povezanost između MMR vakcine i poremećaja iz spektra autizma, čak ni kod dece sa visokim rizikom, čija braća ili sestre imaju dijagnostikovan PSA. Pored toga, određeni simptomi PSA mogu se uočiti i pre primene prve doze MMR vakcine [3,6,7]. Ovo oklevanje i dalje doprinosi pojavi epidemija bolesti koje se mogu sprečiti vakcinacijom, posebno morbila [2].

Epidemiološka Situacija Morbila

Srbija je poslednju veliku epidemiju morbila doživela tokom 2017–2018. godine, kada je prijavljeno 5.798 slučajeva, uz 15 smrtnih ishoda, uključujući odojčad i druge vulnerabilne osobe [8,9]. Komplikacije su bile česte, naročito kod male dece, a poznato je da morbili mogu izazvati ozbiljne ishode, kao što su pneumonija, koja predstavlja najčešću komplikaciju, i encefalitis, koji je redak, ali težak oblik komplikacije. Epidemija je prvenstveno zahvatila nevakcinisane osobe ili osobe sa nepoznatim vakcinalnim statusom [10].

Glavni uzrok epidemije u Srbiji, kao i u drugim evropskim zemljama, bio je pad obuhvata vakcinacijom. Tokom ovog perioda obuhvat MMR vakcinacijom pao je na približno 70–75%, što je značajno ispod nivoa potrebnog za održavanje kolektivnog imuniteta [11]. Za sprečavanje budućih epidemija morbila neophodan je obuhvat vakcinacijom od najmanje 95% kako bi se održao kolektivni imunitet [12].

INTRODUCTION

Immunization is one of medicine's greatest achievements and remains the most effective way to prevent infectious diseases [1]. Thanks to immunization, millions of children and adults have been protected from severe illness and death [1]. However, alongside immunization's success, doubts, mistrust, and fear of adverse events have contributed to vaccine hesitancy and the re-emergence of vaccine-preventable diseases, particularly measles, in several countries [2].

In some cases, the fear of potential adverse effects has even surpassed the fear of the complications caused by the diseases themselves [3]. One of the most persistent sources of vaccine-related mistrust has been the combined measles, mumps, and rubella (MMR) vaccine [3]. The MMR vaccine, which protects against measles, mumps, and rubella, has been administered for decades [1]. This mistrust originated in 1998 when Andrew Wakefield published an article in *The Lancet*, claiming a supposed link between the MMR vaccine and the onset of autism spectrum disorder (ASD) [3–5].

Wakefield's article, which was later retracted and whose findings were never scientifically validated, garnered significant media attention and instilled fear among parents [3–5]. Since then, numerous epidemiological studies have been conducted, all of which have demonstrated no association between the MMR vaccine and autism spectrum disorder, even in high-risk children who have siblings diagnosed with ASD. Moreover, certain symptoms of ASD can be observed even before the first dose of the MMR vaccine is administered [3,6,7]. This hesitancy continues to contribute to outbreaks of vaccine-preventable diseases, particularly measles [2].

Epidemiological situation of measles

Serbia experienced its most recent major measles outbreak during 2017–2018, when 5,798 cases were reported, with 15 deaths recorded, including infants and other vulnerable individuals [8,9]. Complications were frequent, particularly among young children, and measles is known to cause serious outcomes such as pneumonia (the most common complication) and encephalitis (a rare but severe complication). The outbreak primarily affected unvaccinated individuals or those with unknown vaccination status [10].

The main cause of the epidemic in Serbia, as well as in other European countries, was a decline in vaccination coverage. During this period, MMR vaccine coverage dropped to approximately 70–75%, which is significantly below the level required for herd immunity [11]. To prevent future outbreaks, measles requires at least 95% vaccination coverage to maintain herd immunity [12].

Pre uvođenja široko rasprostranjene vakcinacije, morbili su širom sveta uzrokovali milione smrtnih ishoda svake godine. Programi vakcinacije su od tada sprečili procenjenih nekoliko desetina miliona smrtnih ishoda širom sveta [13]. Zbog nedovoljnog obuhvata vakcinacijom i ciklične prirode epidemija morbila, Srbija i dalje ostaje u riziku od budućih epidemija ukoliko ne bude održavala visok nivo imunizacije [11].

Pregled poremećaja iz spektra autizma

Poremećaj iz spektra autizma (PSA) predstavlja neurorazvojni poremećaj koji karakterišu trajni deficiti u socijalnoj komunikaciji i socijalnoj interakciji, zajedno sa ograničenim i repetitivnim obrascima ponašanja, interesovanja ili aktivnosti. Simptomi počinju u ranom detinjstvu, ometaju svakodnevno funkcionisanje i značajno variraju po težini. Simptomi su obično evidentni u ranom detinjstvu, a PSA se često može pouzdano dijagnostikovati između 18. i 24. meseca života [14].

Etiologija PSA je složena i multifaktorijalna. Dosadašnji dokazi ukazuju na to da genetski faktori imaju dominantnu ulogu, dok faktori sredine, naročito prenatalni i perinatalni faktori, mogu doprineti riziku za razvoj PSA kroz interakciju sa genetskom predispozicijom [15].

Prijavljena prevalencija poremećaja iz spektra autizma značajno je porasla tokom poslednjih nekoliko decenija [16]. Rana epidemiološka istraživanja sprovedena tokom 1960-ih i 1970-ih godina procenjivala su prevalenciju PSA na 0,5–0,7 na 10.000 dece. Do početka 1990-ih, prijavljena prevalencija porasla je na približno 3,3–16 na 10.000, što je odražavalo poboljšanje identifikacije slučajeva i promene dijagnostičkih koncepata, a ne stvarnu epidemiju ovog poremećaja [16].

Nakon toga, izmene dijagnostičkih kriterijuma, povećana informisanost javnosti i stručnjaka, širi programi skrininga i bolja dostupnost dijagnostičkih usluga doprineli su značajnom porastu prijavljene prevalencije širom sveta [17,18]. Prema ažuriranom sistematskom pregledu koji su sproveli Zeidan i sar., a koji je obuhvatio istraživanja iz 34 zemlje objavljena između 2012. i 2021. godine, medijana globalne prevalencije PSA iznosi približno 100 na 10.000 dece (1%). Međutim, prijavljene procene značajno variraju, od 1,09 do 436 na 10.000, u zavisnosti od metodologije istraživanja, geografskog regiona i zdravstvene infrastrukture [17].

Slično tome, Talantseva i sar. pokazali su zbirnu globalnu prevalenciju od približno 0,72%, pri čemu su najviše procene zabeležene u zemljama sa visokim prihodima i Severnoj Americi [18]. Nedavni podaci sistema nadzora iz Sjedinjenih Američkih Država dodatno ilustruju povećanje broja identifikovanih slučajeva PSA. Prema podacima CDC Autism and Developmental

Before widespread vaccination, measles caused millions of deaths globally each year. Vaccination programs have since prevented an estimated tens of millions of deaths worldwide [13]. Because of insufficient vaccination coverage and the cyclical nature of measles outbreaks, Serbia remains at risk of future epidemics unless it maintains high immunization rates [11].

Overview of autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by persistent deficits in social communication and social interaction, together with restricted and repetitive patterns of behaviour, interests, or activities. Symptoms begin in early childhood, interfere with everyday functioning, and vary considerably in severity. Symptoms are typically evident in early childhood, and ASD can often be reliably diagnosed between 18 and 24 months of age [14].

The etiology of ASD is complex and multifactorial. Current evidence suggests that genetic factors play the predominant role, while environmental influences, particularly prenatal and perinatal factors, may contribute to ASD risk through interaction with genetic susceptibility [15].

The reported prevalence of autism spectrum disorder has increased substantially over the past several decades [16]. Early epidemiological studies conducted during the 1960s and 1970s estimated ASD prevalence to range between 0.5 and 0.7 per 10,000 children. By the early 1990s, reported prevalence had increased to approximately 3.3–16 per 10,000, reflecting improvements in case identification and evolving diagnostic concepts rather than a true epidemic of the disorder [16].

Subsequently, revisions of diagnostic criteria, increased public and professional awareness, broader screening programs, and improved access to diagnostic services have contributed to a marked rise in reported prevalence worldwide [17,18]. According to the updated systematic review by Zeidan et al., which included studies from 34 countries published between 2012 and 2021, the median global prevalence of ASD is approximately 100 per 10,000 children (1%). However, reported estimates vary considerably, ranging from 1.09 to 436 per 10,000 depending on study methodology, geographic region, and healthcare infrastructure [17].

Similarly, Talantseva et al. demonstrated a pooled global prevalence of approximately 0.72%, with the highest estimates reported in high-income countries and North America [18]. Recent surveillance data from the United States further illustrate the increasing number of identified ASD cases. According to the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Net-

Disabilities Monitoring (ADDM) Network, kod približno jednog od 31 deteta uzrasta od 8 godina identifikovan je PSA u 2022. godini. Međutim, ove procene odražavaju podatke nadzora iz odabranih zajednica u SAD i ne treba ih tumačiti kao globalnu prevalenciju.

Razlike u procenama prevalencije uglavnom se pripisuju razlikama u dijagnostičkoj praksi, identifikaciji slučajeva, nivou informisanosti i dostupnosti zdravstvenih usluga [19]. Aktuelni dokazi ukazuju na to da je veliki deo uočenog porasta prevalencije PSA posledica promena u dijagnostičkoj praksi, veće informisanosti i bolje identifikacije slučajeva, a ne jednog jedinstvenog uzročnog faktora. Ipak, istraživači i dalje ispituju doprinos faktora sredine i demografskih faktora [18].

Imunizacija

Imunizacija je jedna od najefikasnijih javnozdravstvenih intervencija u prevenciji zaraznih bolesti putem primene vakcina, koje stimulišu imunski sistem da razvije dugotrajni zaštitni imunitet. Visok obuhvat vakcinacijom obezbeđuje kako individualnu zaštitu, tako i kolektivni imunitet, čime se smanjuje prenošenje bolesti i sprečava pojava epidemija [1,20]. Vakcinacija predstavlja jednu od najstarijih medicinskih praksi u prevenciji bolesti [21].

Prvu uspešnu vakcinu razvio je Edward Jenner 1796. godine protiv velikih boginja. Ubrizgavanjem virusa kravljih boginja zdravim osobama, Jenner je uočio razvoj imuniteta protiv velikih boginja. Budući da je prva vakcina bila dobijena od virusa kravljih boginja, termin *vakcina* potiče od latinske reči *vacca*, što znači „krava" [22].

Vakcinacija je značajno doprinela smanjenju smrtnosti na globalnom nivou od bolesti koje se mogu sprečiti vakcinacijom, naročito među decom. Vakcinacijom velikog dela populacije razvija se kolektivni imunitet. Ovaj mehanizam prekida prenošenje mikroorganizma odgovornog za nastanak bolesti. Budući da mnogi infektivni uzročnici zavise od osetljivih domaćina za nastavak prenosa, visok nivo imuniteta populacije smanjuje njihovu cirkulaciju i štiti vulnerabilne osobe koje iz medicinskih razloga ne mogu biti vakcinisane [22,23].

U Republici Srbiji, Zakon o zaštiti stanovništva od zaraznih bolesti reguliše obaveznu i preporučenu aktivnu imunizaciju [24].

MMR Vakcina

MMR vakcina je kombinovana živa atenuisana vakcina koja štiti od morbila, zaušaka i rubeole indukovanjem trajnog imunskog odgovora. Pokazala je visoku efikasnost, dugotrajnu imunogenost i odličan bezbednosni profil, zbog čega predstavlja osnovu rutinskih programa imunizacije dece širom sveta [1,25,26].

work, approximately 1 in 31 children aged 8 years were identified with ASD in 2022. However, these estimates reflect surveillance data from selected U.S. communities and should not be interpreted as global prevalence.

Differences in prevalence estimates are largely attributed to variations in diagnostic practices, case ascertainment, awareness, and access to healthcare services [19]. Current evidence suggests that much of the observed increase in ASD prevalence is attributable to changes in diagnostic practices, greater awareness, and improved ascertainment rather than a single causal factor. However, researchers continue to investigate the contribution of environmental and demographic influences [18].

Immunization

Immunization is one of the most effective public health interventions for preventing infectious diseases through vaccine administration, which stimulates the immune system to develop long-lasting protective immunity. High vaccination coverage provides both individual protection and herd immunity, thereby reducing disease transmission and preventing outbreaks [1,20]. Vaccination represents one of the oldest medical practices for disease prevention [21].

The first successful vaccine was developed by Edward Jenner in 1796 against smallpox. By injecting healthy individuals with the cowpox virus, Jenner observed the development of immunity to smallpox. Because the first vaccine was derived from the cowpox virus, the term *vaccine* originates from the Latin word *vacca*, meaning *cow* [22].

Vaccination has contributed substantially to the global reduction in mortality from vaccine-preventable diseases, particularly among children. By vaccinating a large portion of the population, herd immunity develops. This mechanism disrupts the transmission of the microorganism responsible for the disease. Because many infectious agents rely on susceptible hosts for continued transmission, high population immunity reduces their circulation and protects vulnerable individuals who cannot be vaccinated for medical reasons [22,23].

In the Republic of Serbia, the Law on the Protection of the Population from Infectious Diseases regulates mandatory and recommended active immunization [24].

MMR Vaccine

The MMR vaccine is a combined live-attenuated vaccine that protects against measles, mumps and rubella by inducing a durable immune response. It has demonstrated high effectiveness, long-term immunogenicity and an excellent safety profile, making it a cornerstone of routine childhood immunization programs worldwide [1,25,26].

Zauške mogu dovesti do muške neplodnosti, dok rubeola predstavlja ozbiljan rizik za trudnice i fetus u razvoju. Vakcinacija značajno smanjuje učestalost ovih bolesti i težinu njihovih komplikacija, od kojih neke mogu ugroziti život [27,28].

U Srbiji se MMR vakcina primenjuje u dve doze. Prema nacionalnom kalendaru imunizacije, prva doza se daje između 12. i 15. meseca života, iako pojedini izvori dozvoljavaju njenu primenu do 18. meseca. Iako se prva doza još uvek može primeniti tokom druge godine života, nije preporučljivo odlagati vakcinaciju, jer se time povećava rizik od obolevanja od neke od ovih bolesti pre imunizacije.

Druga doza, odnosno revakcinacija, daje se pre polaska u školu (prvi razred) kako bi se obezbedio potpun imunitet. Brojna istraživanja potvrdila su efikasnost, značaj i bezbednost MMR vakcine, zbog čega je ona deo obaveznog kalendara imunizacije [24].

Roditelji i vakcinacija

Oklevanje u vezi sa vakcinacijom postoji još od uvođenja prvih vakcina, ali je poslednjih godina sve više pod uticajem dezinformacija, društvenih mreža i opadanja poverenja u naučne i javnozdravstvene institucije [1,2].

Objavljivanje Wakefieldove studije iz 1998. godine, koja je iznela nepotkrepljenu tvrdnju o povezanosti između MMR vakcine i autizma, značajno je pojačalo zabrinutost javnosti i doprinelo smanjenju poverenja u imunizaciju dece, uprkos njenom kasnijem povlačenju iz publikacije i naučnoj diskreditaciji [4,5].

Roditelji su često izloženi protivrečnim informacijama o bezbednosti vakcina, neželjenim događajima i rasporedu vakcinacije, što može uticati na odluke o imunizaciji [1,2]. Međutim, brojna epidemiološka istraživanja sprovedena tokom prethodne dve decenije dosledno su pokazala da ne postoji povezanost između MMR vakcinacije i poremećaja iz spektra autizma [6,7,29].

Javnozdravstvene institucije i dalje naglašavaju da je visok obuhvat vakcinacijom od suštinskog značaja za sprečavanje epidemija bolesti koje se mogu sprečiti vakcinacijom i zaštitu vulnerabilnih populacija [1,2].

MMR vakcina i poremećaj iz spektra autizma (PSA)

Zabrinutost zbog moguće povezanosti između MMR vakcine i poremećaja iz spektra autizma (PSA) potekla je od sada diskreditovane studije koju su 1998. godine objavili Andrew Wakefield i saradnici. Studija je obuhvatila samo dvanaestoro dece, od kojih je osmoro imalo dijagnostikovan PSA.

Autori su pretpostavili da MMR vakcina može izazvati inflamaciju creva, omogućavajući štetnim supstancama da dospeju u krvotok i deluju na centralni nervni sistem, čime bi potencijalno doprinele razvoju autizma [4,5]. Međutim, studija je imala ozbiljna meto-

Mumps can lead to male infertility, while rubella poses a serious risk to pregnant women and the developing fetus. Vaccination significantly reduces both the incidence of these diseases and the severity of their complications, some of which can be life-threatening [27,28].

In Serbia, the MMR vaccine is administered in two doses. According to the national immunization schedule, the first dose is given between 12 and 15 months of age, although some sources allow administration up to 18 months. While the first dose can still be given during the second year of life, it is not advisable to delay, as this increases the risk of contracting one of these diseases before immunization.

The second dose, or booster, is given before school entry (first grade) to ensure full immunity. Numerous studies have confirmed the efficacy, importance, and safety of the MMR vaccine, which is why it is part of the mandatory immunization schedule [24].

Parents and Vaccination

Vaccine hesitancy has existed since the introduction of the first vaccines but has become increasingly influenced by misinformation, social media, and declining trust in scientific and public health institutions [1,2].

The publication of Wakefield's 1998 study, which proposed an unsupported association between the MMR vaccine and autism, substantially amplified public concern and contributed to declining confidence in childhood immunization despite its subsequent retraction and scientific discrediting [4,5].

Parents are often exposed to conflicting information about vaccine safety, adverse events, and vaccination schedules, which may influence immunization decisions [1,2]. However, extensive epidemiological studies conducted over the past two decades have consistently demonstrated no association between MMR vaccination and autism spectrum disorder [6,7,29].

Public health authorities continue to emphasize that high vaccination coverage is essential to prevent outbreaks of vaccine-preventable diseases and protect vulnerable populations [1,2].

MMR Vaccine and Autism Spectrum Disorder (ASD)

Concerns regarding a potential association between the MMR vaccine and autism spectrum disorder (ASD) originated from a now-discredited study published in 1998 by Andrew Wakefield and colleagues. The study included only twelve children, eight of whom were diagnosed with ASD.

The authors hypothesized that the MMR vaccine could cause intestinal inflammation, allowing harmful substances to enter the bloodstream and affect the central nervous system, ultimately contributing to the

dološka ograničenja, uključujući izuzetno mali uzorak, odsustvo kontrolne grupe i nepostojanje dokaza koji bi utvrdili vremensku povezanost između gastrointestinalnih nalaza i pojave PSA.

Naknadna istraživanja otkrila su ozbiljna kršenja etičkih principa i neprijavljene finansijske sukobe interesa, uključujući Wakefieldovo učešće u razvoju alternativne vakcine protiv morbila. Članak je 2010. godine formalno povučen iz publikacije, a Wakefield je zbog profesionalnog nedoličnog postupanja brisan iz registra lekara Ujedinjenog Kraljevstva [5,30,31].

Uprkos povlačenju rada, njegova publikacija imala je dubok i dugotrajan globalni uticaj, značajno narušavajući poverenje javnosti u MMR vakcinu i doprinoseći dugotrajnom oklevanju u vezi sa vakcinacijom u mnogim zemljama [1,29].

Hipoteza je privukla pažnju javnosti delimično zbog toga što se rani simptomi PSA često javljaju između 18. i 24. meseca života, što se vremenski podudara sa periodom kada se MMR vakcina rutinski primenjuje. Ova vremenska povezanost doprinela je zabrinutosti roditelja, uprkos odsustvu naučnih dokaza koji bi podržali uzročnu povezanost.

Tokom prethodne dve decenije brojna velika epidemiološka istraživanja sprovedena u različitim zemljama i populacijama dosledno su pokazala da MMR vakcinacija ne povećava rizik od PSA. Jedno od prvih epidemioloških istraživanja, sprovedeno u Ujedinjenom Kraljevstvu, nije pronašlo dokaze o uzročnoj povezanosti između MMR vakcinacije i autizma [29].

Nakon toga, Madsen i saradnici sproveli su veliku populacionu kohortnu studiju u Danskoj koja je obuhvatila 537.303 dece. Studija nije pokazala statistički značajnu razliku u incidenciji PSA između vakcinisane i nevakcinisane dece [32].

Dodatne kohortne studije i studije tipa slučaj-kontrola sprovedene u Ujedinjenom Kraljevstvu, Sjedinjenim Američkim Državama, Finskoj i Japanu dodatno su potvrdile ove nalaze, pri čemu nijedna od njih nije pokazala povezanost između MMR vakcinacije i PSA [33–35]. Nadalje, nacionalna kohortna studija sprovedena u Danskoj i objavljena 2019. godine, koja je obuhvatila 657.461 dete, potvrdila je da MMR vakcinacija ne povećava rizik od autizma, čak ni među decom koja se smatraju rizičnijom zbog porodičnih ili faktora sredine [7].

Prirodni populacioni eksperiment sproveden u Japanu dodatno je doveo u pitanje pretpostavljenu povezanost između MMR vakcinacije i PSA. Nakon povlačenja MMR vakcine iz nacionalnog programa imunizacije, istraživači su ispitivali da li se incidencija PSA smanjila uporedo sa smanjenjem stope vakcinacije. Međutim, uprkos smanjenom obuhvatu MMR vakcinacijom, prevalencija PSA je nastavila da raste, što je bilo u suprotnosti sa hipotezom o uzročnoj povezanosti [36,37].

development of autism [4,5]. However, the study had major methodological limitations, including an extremely small sample size, no control group, and no evidence establishing a temporal relationship between gastrointestinal findings and ASD onset.

Subsequent investigations revealed serious ethical violations and undisclosed financial conflicts of interest, including Wakefield's involvement in developing an alternative measles vaccine. In 2010, the article was formally retracted, and Wakefield was removed from the UK medical register due to professional misconduct [5,30,31].

Despite its retraction, the publication had a profound and long-lasting global impact, substantially undermining public confidence in the MMR vaccine and contributing to persistent vaccine hesitancy in many countries [1,29].

The hypothesis gained public attention partly because early symptoms of ASD commonly emerge between 18 and 24 months of age, which coincides with the period when the MMR vaccine is routinely administered. This temporal association contributed to parental concern despite the absence of scientific evidence supporting causation.

Over the past two decades, numerous large-scale epidemiological studies conducted in different countries and populations have consistently demonstrated that MMR vaccination does not increase the risk of ASD. One of the earliest epidemiological investigations, conducted in the United Kingdom, found no evidence of a causal association between MMR vaccination and autism [29].

Subsequently, Madsen et al. conducted a large population-based cohort study in Denmark that included 537,303 children. The study demonstrated no statistically significant difference in ASD incidence between vaccinated and unvaccinated children [32].

Additional cohort and case-control studies in the United Kingdom, the United States, Finland, and Japan reinforced these findings, consistently failing to show an association between MMR vaccination and ASD [33–35]. Furthermore, a nationwide Danish cohort study published in 2019 involving 657,461 children confirmed that MMR vaccination does not increase the risk of autism, even among children considered at higher risk due to familial or environmental factors [7].

A natural population-based experiment conducted in Japan further challenged the proposed association between MMR vaccination and ASD. After the MMR vaccine was withdrawn from the national immunization program, researchers examined whether ASD incidence declined alongside reduced vaccination rates. However, despite decreased MMR uptake, ASD prevalence continued to increase, contradicting the hypothesis of a causal relationship [36,37].

Slično tome, istraživanje sprovedeno u Kaliforniji analiziralo je trendove u obuhvatu MMR vakcinacijom i dijagnozama autizma u periodu od 1980. do 1994. godine. Iako su stope MMR vakcinacije tokom ovog perioda porasle, nije uočeno odgovarajuće povećanje prevalencije PSA koje bi se moglo pripisati vakcinaciji [38].

Naknadna zabrinutost bila je usmerena na komponente vakcina, naročito na tiomersal, konzervans koji sadrži živu i koji se ranije koristio u nekim vakcinama radi sprečavanja bakterijske kontaminacije u višedoznim bočicama. Iako nijedan dokaz nije podržao povezanost između izloženosti tiomersalu i autizma, ovo jedinjenje je iz predostrožnosti uklonjeno iz većine vakcina namenjenih deci u Sjedinjenim Američkim Državama. Naknadne studije pokazale su da je prevalencija PSA nastavila da raste i nakon uklanjanja tiomersala, pružajući dodatne dokaze protiv uzročne povezanosti [39].

Istraživači su takođe ispitivali da li kumulativna izloženost antigenima iz vakcina tokom ranog detinjstva može doprineti razvoju PSA. Studija tipa slučaj-kontrola, koja je procenjivala izloženost antigenima tokom prve dve godine života, nije pokazala povećan rizik od PSA kod dece izložene većem broju antigena iz vakcina u poređenju sa kontrolnom grupom [40].

Naučni dokazi nisu potvrdili zabrinutost da primena više vakcina u skladu sa preporučenim kalendarom imunizacije može negativno uticati na neurorazvoj. Studije koje su upoređivale decu vakcinisanu prema preporučenom kalendaru sa decom kod koje je vakcinacija odložena nisu pokazale razlike u neuropsihološkim ili razvojnim ishodima, dok je odlaganje vakcinacije povećalo osetljivost na bolesti koje se mogu sprečiti vakcinacijom [41].

Pored ovih ključnih epidemioloških istraživanja, noviji dokazi dodatno su ojačali zaključak da MMR vakcinacija nije povezana sa PSA. Jain i sar. pokazali su da MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA čak ni kod dece čija su starija braća ili sestre imali dijagnostikovan autizam, odnosno kod populacije koja se smatra populacijom sa povećanim porodičnim rizikom [6].

Slično tome, Goin-Kochel i saradnici nisu pronašli razlike u obrascima vakcinacije između dece sa PSA i kontrolne grupe koje bi podržale uzročnu povezanost između vakcinacije i autizma [42]. Eksperimentalni dokazi takođe su dodatno potvrdili ove nalaze. Gadad i sar. izvestili su da primena vakcina koje sadrže tiomersal kod mladunaca rezus makakija nije dovela do ponašanja sličnog autizmu niti do neuropatoloških abnormalnosti [43].

Nadalje, sveobuhvatni sistematski pregled koji su sproveli Modabbernia i sar. zaključio je da PSA nastaje kao rezultat složene interakcije genetskih faktora i faktora sredine. Istovremeno, nema dokaza koji podržavaju vakcinaciju kao faktor rizika za autizam [15] **(**Tabela 1**).**

Similarly, a study conducted in California analyzed trends in MMR vaccination coverage and autism diagnoses between 1980 and 1994. Although MMR vaccination rates increased during this period, no corresponding increase in ASD prevalence attributable to vaccination was observed [38].

Additional concerns later focused on vaccine components, particularly thimerosal, a mercury-containing preservative previously used in some vaccines to prevent bacterial contamination in multidose vials. Although no evidence supported an association between thimerosal exposure and autism, the compound was removed from most childhood vaccines in the United States as a precautionary measure. Subsequent studies demonstrated that ASD prevalence continued to rise even after thimerosal removal, providing further evidence against a causal association [39].

Researchers have also investigated whether cumulative exposure to vaccine antigens during early childhood could contribute to ASD development. A case-control study evaluating antigen exposure during the first two years of life found no increased risk of ASD among children exposed to more vaccine antigens than controls [40].

Scientific evidence has not supported concerns that administering multiple vaccines according to the recommended immunization schedule could negatively affect neurodevelopment. Studies comparing children vaccinated according to the recommended schedule with those receiving delayed vaccinations found no differences in neuropsychological or developmental outcomes, while delayed vaccination increased susceptibility to vaccine-preventable diseases [41].

In addition to these landmark epidemiological studies, more recent evidence has further strengthened the conclusion that MMR vaccination is not associated with ASD. Jain et al. demonstrated that MMR vaccination was not associated with an increased risk of ASD even among children with older siblings diagnosed with autism, a population considered to be at increased familial risk [6].

Similarly, Goin-Kochel et al. found no differences in vaccination patterns between children with ASD and controls that would support a causal relationship between vaccination and autism [42]. Experimental evidence has also reinforced these findings. Gadad et al. reported that administering thimerosal-containing vaccines to infant rhesus macaques did not result in autism-like behavior or neuropathological abnormalities [43].

Furthermore, a comprehensive systematic review by Modabbernia et al. concluded that ASD arises from a complex interaction between genetic and environmental factors. At the same time, no evidence supports vaccination as a risk factor for autism [15] **(**Table 1**).**

Tabela 1. Najznačajnije epidemiološke studije koje su ispitivale povezanost između MMR vakcinacije i poremećaja iz spektra autizma (PSA)

Table 1. Major epidemiological studies investigating the association between MMR vaccination and ASD

Studija */Study*	**Zemlja** */ Country*	**Dizajn studije / Veličina uzorka /** ***Study design / Sample size***	**Glavni nalazi** */ Main findings*
Taylor et al., 2014 [29]	United Kingdom	Epidemiological study	Nije utvrđena uzročna povezanost između MMR vakcinacije I autizma / *No causal association between MMR vaccination and autism*
Madsen et al., 2002 [32]	Denmark	Cohort study, 537,303 children	Nije utvrđen povećan rizik od PSA kod vakcinisane dece / *No increased risk of ASD among vaccinated children*
Smeeth et al., 2004 [34]	United Kingdom	Case-control study	Nije utvrđena povezanost između MMR vakcinacije i pervazivnih razvojnih poremećaja / *No association between MMR vaccination and pervasive developmental disorders*
Honda et al., 2005 [36]	Japan	Population-based study	Incidencija PSA nastavila je da raste nakon povlačenja MMR vakcine / *ASD incidence continued to rise after MMR withdrawal*
Hviid et al., 2019 [7]	Denmark	Nationwide cohort study, 657,461 children	MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA / *MMR vaccination not associated with increased ASD risk*
Jain et al., 2015 [6]	United States	Retrospective cohort study, 95,727 children	MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA, uključujući i decu čiji je stariji brat ili sestra imao/la PSA / *MMR vaccination was not associated with increased ASD risk, including among children with an older sibling with ASD*

Sveukupno, dokazi dobijeni iz velikih epidemioloških studija, sistematskih pregleda, meta-analiza, eksperimentalnih istraživanja i nacionalnih kohortnih studija sprovedenih tokom više od dve decenije dosledno pokazuju da MMR vakcinacija nije povezana sa povećanim rizikom od PSA. Velike međunarodne zdravstvene organizacije, uključujući Svetsku zdravstvenu organizaciju (SZO) i Centre za kontrolu i prevenciju bolesti (CDC), i dalje podržavaju ove nalaze i potvrđuju da je MMR vakcina bezbedna i da ne izaziva autizam [24].

ZAKLJUČAK

Pad stope MMR vakcinacije i povećanje prevalencije poremećaja iz spektra autizma (PSA) jasno pokazuju da između ova dva fenomena ne postoji uzročna povezanost. Brojna epidemiološka istraživanja, kliničke studije i literatura zasnovana na dokazima detaljno su opovrgli ovu široko rasprostranjenu zabludu.

MMR vakcina, kao i druge vakcine, ne utiče na neuropsihološki razvoj dece i ostaje veoma efikasna u prevenciji zaraznih bolesti. Sa smanjenjem stope imunizacije povećava se rizik od nove epidemije morbila, a istraživači predviđaju da bi do nje moglo doći u bliskoj budućnosti.

Stav Svetske zdravstvene organizacije (SZO) je jasan: vakcinacija ne štiti samo pojedinca, već i čitavu zajednicu, doprinoseći eliminaciji i iskorenjivanju mnogih smrtonosnih bolesti jednom zauvek.

Sukob interesa: Nije prijavljen.

Collectively, evidence from large epidemiological studies, systematic reviews, meta-analyses, experimental investigations and nationwide cohort studies conducted over more than two decades consistently demonstrates that MMR vaccination is not associated with an increased risk of ASD. Major international health organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), continue to endorse these findings and affirm that the MMR vaccine is safe and does not cause autism [24].

CONCLUSION

The declining MMR vaccination rate and the increasing prevalence of autism spectrum disorder (ASD) clearly demonstrate that there is no causal link between the two. Numerous epidemiological studies, clinical research, and evidence-based literature have thoroughly disproven this widespread misconception.

The MMR vaccine, like all other vaccines, does not affect children's neuropsychological development and remains highly effective at preventing infectious diseases. As immunization rates decline, the risk of a new measles outbreak is rising, and researchers predict one may occur in the near future.

The World Health Organization (WHO) position is clear: vaccination not only protects the individual but also safeguards the entire community, helping eliminate and eradicate many deadly diseases once and for all.

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