
Neurological disorders associated with Measles-Mumps-Rubella vaccination- a review

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Abstract: *Background:* The safety of the measles-mumps-rubella (MMR) vaccine has always been doubtful due to its side effects reported over time. Current criticism revolves around the fact that the trials were too small and did not follow up on children involved in the study for long enough periods to determine if there would be any potential hazards involved. *Objective:* To assess the risks of seizures and other neurological events following MMR immunization in children up to 16 years of age. *Methodology:* The data was collected from retrospective and prospective cohort studies carried out worldwide on around 8 million children who received MMR immunization up to their 16 years of life. About 110 published articles (from 1991 to 2014), satisfied the inclusion criteria and 38 of them were included in the review. *Main Results:* MMR immunization was associated with consistent increase in febrile seizures in the 7- through 14-day interval. Delaying MMR vaccine past 15 months of age resulted in a higher risk of seizures. The long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology. The reports on other neurological disorders included the rare adverse events of aseptic meningitis associated with a form of the MMR vaccine containing the Urabe mumps strain, and very few cases of encephalitis, convulsions, Guillain-Barre syndrome and subacute sclerosing panencephalitis. The most commonly occurring adverse reaction was syncopal fit. *Conclusion:* Measles, mumps, and rubella are all very serious illnesses and can have complications leading to lifetime disability or even death. The long-term effects of the MMR vaccine are still in question, but on comparing its risks and benefits, the benefits far outweigh the incidence of serious adverse events associated with immunization. Changes in the vaccine formulation may help to reduce side-effects, and further advances may help make current vaccines even safer.

Keywords: Immunization, MMR, Neurological Disorders

1. Background

The MMR vaccine (an immunization shot against measles, mumps, and rubella) was first developed by Maurice Hilleman at Merck in the late 1960s [1]. The vaccine is a mixture of three live attenuated viruses, administered via injection. The shot is generally administered to children around the age of one year, with a second dose before starting school (i.e. age 4/5). The second dose is a dose to produce immunity in the small number of persons (2-5%) who fail to develop measles immunity after the first dose [2]. In the United States, the vaccine was licensed in 1971 and the second dose was introduced in 1989 [3]. Since the introduction of its earliest versions in the 1970s, over 500 million doses have been used in over 60 countries. The vaccine is sold by Merck as M-M-R II, GlaxoSmithKline

Biologicals as Priorix, Serum Institute of India as Tresivac, and Sanofi Pasteur as Trimovax. It is usually considered a childhood vaccination. However, it is also recommended for use in some cases of adults with HIV [4,5].

There have been doubts about the safety of the measles-mumps-rubella vaccine due to MMR vaccine side effects reported over time. Recent studies are still falling short of the mark to demonstrate safety issues with this vaccine. Current criticism revolves around the fact that the trials were too small and did not follow up on children involved in the study for long enough periods to determine if there would be any potential hazards involved. In other words, the long-term effects of the MMR vaccine are still in question.

2. Methodology

The data was collected from retrospective and prospective

cohort studies carried out worldwide on around 8 million children who received MMR immunization up to their 16 years of life. The author independently extracted data and assessed methodological quality of the included studies. About 110 published articles (from 1991 to 2014), satisfied the inclusion criteria and 38 of them were included in the review.

3. Studies on the Risks of Seizures and other Neurological Events Following MMR

To evaluate the risks of seizures and other neurologic events following measles-mumps-rubella (MMR) or measles-rubella (MR) immunization, Griffin *et al.* [6] conducted a retrospective cohort study among 18,364 Tennessee children enrolled in Medicaid who received MMR or MR immunizations in their first 3 years of life. One hundred children had seizures at some time between immunization and 36 months but there were no encephalopathies during that period. Four children had febrile seizures in the 7 through 14 days following MMR or MR immunization compared with 72 in the interval 30 or more days following MMR or MR immunization yielding a relative risk (95% confidence interval) of 2.1 (0.7 to 6.4). Although not statistically significant, this increase in febrile seizures in the 7- through 14-day interval following MMR immunization was coincident with the occurrence of fever following MMR immunization and was consistent with reports of other investigators.

As reported by Harnden & Shakespeare, adverse reactions, rarely serious, may occur from each component of the MMR vaccine. 10% of children develop fever, malaise and a rash 5–21 days after the first vaccination; 5% develop temporary joint pain. Older women appear to be more at risk of joint pain, acute arthritis, and even (rarely) chronic arthritis [7,8]. Anaphylaxis is an extremely rare but serious allergic reaction to the vaccine [9]. One cause can be egg allergy [10]. The vaccine product brief lists many other possible adverse reactions [11].

The number of reports on neurological disorders is very small, other than evidence for an association between a form of the MMR vaccine containing the Urabe mumps strain and rare adverse events of aseptic meningitis, a transient mild form of viral meningitis [12]. The UK National Health Service stopped using the Urabe mumps strain in the early 1990s due to cases of transient mild viral meningitis, and switched to a form using the Jeryl Lynn mumps strain instead [13]. The Urabe strain remains in use in a number of countries; MMR with the Urabe strain is much cheaper to manufacture than with the Jeryl Lynn strain, and a strain with higher efficacy along with a somewhat higher rate of mild side effects may still have the advantage of reduced incidence of overall adverse events [14].

In November 1994, 92% of the 7.1 million school children in England aged 5-16 years received measles and rubella

(MR) vaccine [15]. By the end of October 1995, Britain's Committee on Safety of Medicines had received 1202 reports describing 2735 suspected adverse reactions to the vaccines administered in the campaign, among which 530 were serious, though none was fatal. Symptoms and signs of anaphylaxis or allergic reactions within 24 hours of vaccination were reported from 1 in 65000 of those vaccinated. There were 91 reports of serious neurological reactions (including 61 reports of convulsions); but reported rates of encephalitis, convulsions, and Guillain-Barre syndrome were lower than the background prevalence of those conditions. The one report of subacute sclerosing panencephalitis occurred one month after vaccination in a child with a history of mild measles infection some years earlier; thus it is unlikely that the vaccine was responsible.

D'Souza *et al.* [16] reported the Adverse Events Following Immunisation (AEFI) associated with measles-mumps-rubella vaccine (MMR) administered as part of the Measles Control Campaign (MCC) conducted in Australia from August to November 1998 resulting in the vaccination of a total of 1.7 million school children. Reports of adverse events that occurred within 30 days of administration of the MMR vaccine were assessed by an expert panel that assigned a causality rating to each AEFI. Reports with missing onset dates or uncertain causality were excluded. Eighty-nine AEFI were classified as associated with MMR vaccine and the overall rate of adverse events was 5.24 per 100,000 doses of vaccine administered. Of these 46 were thought to be certainly caused by MMR vaccine, 23 were probably and 20 were possibly associated with the vaccine. Although 46 reactions were categorized to be certainly caused by the MMR vaccine, the majority of these were syncopal fits, syncope, local reactions, and allergic reactions that were short-lived, and all of these children recovered. The most commonly occurring adverse reaction was syncopal fit with a rate of 1.24 per 100,000. There was only one anaphylactic reaction, giving a rate of 0.06 per 100,000. The combined rate for anaphylaxis, anaphylactoid and allergic reactions was 1.06 per 100,000 administered doses. The rate of seizures (febrile and afebrile) was 0.30 and encephalopathy was 0.06 per 100,000 doses administered. Of the 89 children who had an AEFI, 43 did not require hospitalization or medical attention while 13 were seen in an emergency room, 14 were hospitalized and 19 were seen by a doctor. There were no deaths reported resulting from the administration of the MMR vaccine during the period of the campaign. All children who had an AEFI, recovered although 9 children could not be followed up for reasons of confidentiality. The overall rate of adverse events was lower than that observed in the 1994 measles campaign conducted in the United Kingdom.

Barlow *et al.* in 2001 conducted a cohort study at four large health maintenance organizations and included reviews of the medical records of children with seizures [17]. They calculated the relative risks of febrile and nonfebrile seizures among children after 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile

seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities. Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). The number of febrile seizures attributable to the administration of MMR vaccine was estimated to be 25 to 34 per 100,000 children. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities.

Davis and Barlow summarized data from the Vaccine Safety Datalink Study and other studies that suggested that MMR vaccine is associated with a transiently increased risk of febrile seizures, and causes between 25-34 additional extra febrile seizures per 1,00,000 immunized children [18]. They also discussed some methodological challenges in studies of vaccines and seizures. Because there is no adequate comparison group that would allow for the study of seizures long after vaccination, studies of seizures are limited to acute events shortly following vaccination. Additionally, while seizures following vaccination are worrisome to parents and physicians alike, observational studies of the neurodevelopment outcomes of these children are particularly problematic.

Jefferson *et al.* [19] concluded that the design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunization with MMR cannot be separated from its role in preventing the target diseases.

Vestergaard *et al.* [20] estimated incidence rate ratios (RRs) and risk differences of febrile seizures following MMR vaccination within subgroups of children and evaluated the clinical outcome of febrile seizures following vaccination. They observed that MMR vaccination was associated with a transient increased rate of febrile seizures but the risk difference was small even in high-risk children. The long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology. Miller *et al.* demonstrated the power of active post marketing surveillance to identify or exclude events too rare to be detected in pre licensure trials [21].

With an aim to evaluate the incidence of adverse events following immunization (AEFIs) after routine administration of the MMR vaccine in Iran, Esteghamati *et al.* [22] conducted a study in five provinces among children aged 12 months and 4-6 years of age. During the follow-up period, trained providers reported 792 AEFIs. Parotitis was the most frequent event occurring in 1.8% of recipients. Of 14,109 children vaccinated at 12 months of age the following AEFIs occurred: parotitis (147), fever and convulsions (8), convulsions (7), encephalopathy (1), and anaphylactic reactions (1). Of 29,338 children vaccinated at 4 to 6 years of age, parotitis, fever and convulsions, encephalopathy, and

anaphylaxis occurred in 626, 5, 1, and 1 child, respectively; no convulsions without fever were reported in this age group. Incidence rates of AEFIs following MMR vaccination in Iran were similar to rates of AEFIs reported in other studies.

Wilson *et al.* found significantly elevated risks of primarily emergency room visits approximately one to two weeks following 12 and 18 month vaccination [23]. They suggested future studies to predict or prevent the events.

A new combination vaccine against measles, mumps, rubella and varicella (MMRV) from GlaxoSmithKline Biologicals was reported by Knuf *et al.* in 2008 [24]. It combined the components from two well-established, live, attenuated vaccines against measles, mumps and rubella. A higher incidence of low-grade fever was noted following the first dose of MMRV vaccine, although it was no different from component vaccines following the second dose. MMRV vaccines were recommended in Germany in 2006 for administration in two doses to children aged 11-14 months and 15-23 months. They offered a convenient way to implement varicella vaccination and to achieve high vaccine coverage rates mirroring those of MMR vaccines. Klein *et al.* found that vaccination with MMRV resulted in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines [25].

O'Leary *et al.* [26] conducted a survey among US pediatricians and family physicians. Response rate was 73% (620/849). Twenty-nine percent of Peds and 74% of FP ($p < 0.001$) were unaware of increased febrile seizure risk after MMRV. After reading an informational statement, 20% of Peds and 7% of FP ($p < 0.001$) would recommend MMRV to a healthy 12-15-month-old child.

In an effort to maximize vaccine acceptance by minimizing adverse events following immunization associated with fever, including seizures, the Advisory Committee on Immunization Practices (ACIP) recommended in 2009 the use of measles, mumps and rubella vaccine (MMR) and varicella vaccines (V) given separately (MMR+V) rather than combination MMRV as the first dose of MMR-containing vaccine to infants.

Ackerson *et al.* [27] evaluated factors associated with continued administration of MMRV as the first dose in many infants despite the ACIP recommendation. Altogether, 30,017 children received the first dose of MMRV or MMR+V at 12 to 23 months of age between May 1, 2010 and April 30, 2011. Of these, 10.2% received MMRV while 89.8% received MMR+V. Their data suggested that while most providers followed the ACIP recommendation to administer MMR and V separately, Pediatric Infectious Disease specialists' vaccination practices may impact compliance with ACIP recommendations by other providers. Further study of the drivers behind the use of MMRV rather than MMR+V as the first dose of measles-containing vaccine is needed to determine if reinforcement or if clarification of ACIP recommendations is needed to elucidate when MMRV might be preferred over MMR+V.

Further, Hanf *et al.* [28] performed Self-controlled case series analyses using an exhaustive SNIIR-AM extraction of

French children aged less than 3 years, to investigate the relationship between MMR immunization and children hospitalizations for febrile convulsions. They suggested a significant increase of febrile convulsions during the 6-11 days period following any MMR immunization (IRR=1.49, 95% CI=1.22, 1.83; $p=0.0001$) and no increase 15-35 days post any MMR immunization (IRR=1.03, 95% CI=0.89, 1.18; $p=0.72$). These results were in accordance with other results obtained from large epidemiologic studies.

Reports of childhood epilepsies in temporal association with vaccination had a great impact on the acceptance of vaccination programs by health care providers. For these reasons the Italian League Against Epilepsy (LICE), in collaboration with other Italian scientific societies decided to generate Guidelines on Vaccinations and Epilepsy [29]. The aim of Guidelines on Vaccinations and Epilepsy was to present recent unequivocal evidence from published reports on the possible relationship between vaccines and epilepsy in order to provide information about contraindications and risks of vaccinations in patients with epilepsy. The following main issues had been addressed: (1) whether contraindications to vaccinations exist in patients with febrile convulsions, epilepsy, and/or epileptic encephalopathies; and (2) whether any vaccinations can cause febrile seizures, epilepsy, and/or epileptic encephalopathies.

In a cohort of 3,23,247 US children from the Vaccine Safety Datalink born from 2004 to 2008, Hambidge *et al.* [30] analyzed the association between the timing of childhood vaccination and the first occurrence of seizure with a self-controlled case series analysis of the first doses of individual vaccines received in the first 2 years of life. They found that there is no increased risk of post vaccination seizure in infants regardless of timing of vaccination. In year 2, delaying MMR vaccine past 15 months of age results in a higher risk of seizures. The strength of the association is doubled with MMRV vaccine.

A new study by Feenstra *et al.* [31] has now identified common genetic variants influencing susceptibility to febrile seizures, including two loci specifically associated with MMR-related events.

4. Discussion

Several studies have evaluated the relation between live virus vaccinations and neurological disorders. The data from the Vaccine Safety Datalink Study and other studies suggests that MMR vaccine has been associated with a transiently increased risk of febrile seizures, and causes between 25-34 additional extra febrile seizures per 1,00,000 immunized children [18]. In year 2, delaying MMR vaccine past 15 months of age results in a higher risk of seizures. The strength of the association is doubled with MMRV vaccine [30]. These findings suggest that on-time vaccination is as safe with regard to seizures as delayed vaccination in the first year of life, and that delayed vaccination in the second year of life is associated with more post vaccination seizures than on-time vaccination. As compared with other children with

febrile seizures that are not associated with vaccination, the children who have febrile seizures after vaccination are not at higher risk for subsequent seizures or neurodevelopmental disabilities [17].

The reported rates of encephalitis, convulsions, and Guillain-Barre syndrome are lower than the background prevalence of these conditions [15]. The most commonly occurring adverse reaction is syncopal fit with a rate of 1.24 per 100,000 [16]. In addition, several case reports of encephalitis occurring after monovalent or combination MMR vaccinations exist, but in most cases causality has not been proved [33]. However, the Urabe mumps vaccine strain has been shown to cause encephalitis [12,34]. The problem of vaccine-associated meningitis has been prominent with the Japanese MMR vaccines. In several cases, mumps virus has been isolated from the cerebrospinal fluid and identified by nucleotide sequencing analysis to be the Urabe vaccine strain [34]. The incidence of meningitis attributable to the Urabe vaccine varies from 3.5 to 166 per 1,00,000 doses [35]. A mass immunization campaign with the Urabe-containing MMR vaccine in Brazil resulted in 58 cases of aseptic meningitis [36]. Rare cases of meningitis have been reported after vaccination with the Jeryl Lynn mumps strain, but causality has not been proved in any of the cases. Mumps virus was isolated from the cerebrospinal fluid of a child with meningitis occurring 21 days after Jeryl Lynn vaccination, but the virus was not reliably identified as wild or vaccine virus [33].

Reliable assessment of causality between immunization and rare disorders is extremely difficult. Therefore, the evidence of several of the suspected adverse effects of MMR vaccination has remained controversial or inconclusive. Nevertheless, significant public concern about adverse events of vaccines clearly exists, and continuous surveillance aiming at distinguishing true adverse events from unrelated, chance occurrences is crucial to maintain public confidence in immunization [37]. Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. Maglione *et al.* [32] systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States and suggested that the adverse events are extremely rare and must be weighed against the protective benefits that this vaccine provides.

Ethical issues pertaining to public health, and specifically immunization activities, are important in the implementation of and the public's response to mandatory vaccination programs. Immunization programs can contribute to the creation of an environment where ethical principles are adequately addressed and therefore facilitate vaccination acceptance through: reviewing and evaluating current vaccination mandates in the relevant health jurisdiction with the goal of modifying them as appropriate to increase their effectiveness and acceptance; increasing the use of noncompulsory vaccination strategies; addressing parental/guardian vaccine safety concerns; enhancing the

public's awareness of vaccine-preventable disease risks; and promoting a better public understanding of herd immunity [38].

5. Conclusion

There will always remain some doubt about the "absolute" safety of childhood vaccine, MMR. Measles, mumps, and rubella are all very serious illnesses. They each can have complications that lead to lifetime disability or even death. For every 1,000 children who get measles, 1 or 2 will die from it. On comparing the risks and benefits of MMR vaccine, the benefits of this Measles Control Campaign far outweigh the incidence of serious adverse events associated with immunization. Reassurance of vaccine safety remains critical for population health. Changes in the vaccine formulation (e.g., whole cell to acellular) may also help to reduce side-effects, and further advances may help make current vaccines even safer.

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