Clinical Article

Pediatric MMR Vaccination Safety

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Abstract

TMeasles, mumps and rubella are viral infections that have the potential to result in globally destructive disorders. Measles, mumps and rubella (MMR) vaccine has helped to dramatically reduce the number of cases of measles, mumps and rubella infection, as well as to reduce the amount of pain and suffering associated with each of these natural infections. The purpose of this study was to analyze the incidence of serious neurologic disorders in a comparative examination between MMR vaccine and a vaccine control group. The Vaccine Adverse Events Reporting System (VAERS) database was analyzed for the incidence rate of permanent brain damage, cerebellar ataxia, autism and mental retardation reported following MMR vaccine and diphtheria, tetanus and whole-cell pertussis (DTwcP) containing-vaccines from 1994 through 2000 in the US. Statistically significant increases in the incidence of serious neurologic disorders following pediatric MMR vaccine in comparison to DTwcP vaccine were found. The potentially globally destructive effects of natural measles, mumps and rubella infections means that continued vaccination is necessary, but improvements in MMR vaccines are needed to improve its safety. *Int Pediatr. 2003;18(2):203-208.*

Key words: autism, mental retardation, MMR, neurodevelopmental disorders, VAERS

Introduction

Measles formerly afflicted nearly all children in the US before they reached adolescence. A viral infection caused by a member of the paramyxovirus group, diagnosis of measles is made clinically on the basis of its signs and symptoms, which include a characteristic rash. The diagnosis may be confirmed by a laboratory test that detects antibodies to the measles virus. The disease can be debilitating, and its complications are among the most serious consequences of childhood exanthematous infections. These include otitis media, croup, diarrhea, hemorrhagic rash, pneumonia, parainfectious encephalitis and subacute sclerosing panencephalitis.[1] The currently used Enders strain measles vaccine is a live, more-attenuated vaccine derived from the Edmonston B strain by 40 passages through chicken embryo cells that are maintained at a lower than optimal temperature.[2]

Unlike measles, mumps is not considered a globally devastating disease. Nevertheless, because of its complications, it was targeted for prevention by use of a vaccine. The complications that prompted this were epididymoorchitis, aseptic meningitis, menigoencephalitis and deafness.[3] The currently used live mumps vaccine in the United States, was developed by passing the Jeryl Lynn strain of mumps through numerous passages in vitro, first in embryonated hen's eggs and then in chicken embryo cells.[4]

Rubella is commonly a mild disease; it afflicts children and young adults. It is characterized by erythematous, maculopapular, discrete rash; postauricular and suboccipital lymphadenopathy; and minimal fever. The disease, caused by an RNA virus belonging to the togavirus family, can be transmitted transplacentally to a fetus, sometimes with devastating results. The incubation period of natural rubella is 14 to 21 days, with the characteristic rash appearing within 14 to 17 days after exposure. The patient is usually asymptomatic in the first week after exposure. By early in the second week, lymphadenopathy becomes apparent and rubella virus can usually be cultured from nasopharyngeal secretions. By the end of the second week, virus is detectable in the blood. After the 14 to 21 day incubation period, a one to five day prodromal illness consisting of malaise, low-grade fever, mild conjunctivitis and, occasionally, arthralgia can occur, but it may be minimal or absent. The rash, in most cases, appears at this time, beginning on the face and neck and spreading quickly to the trunk and extremities. It usually lasts about five days. The current live rubella vaccine, is a human diploid fibroblast vaccine, RA 27/3, that was licensed for use in the United States in 1979.[5]

These three different live viral vaccines are combined to produce the measles, mumps and rubella

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(MMR) vaccine analyzed in this study. The American Academy of Pediatrics recommends that MMR vaccine be given at age 15 months and at entry into middle or junior high school. The Advisory Committee on Immunization Practices recommends that MMR be administered at 15 months and then again at school entry at age four to six years. The strength of the US MMR vaccination program has helped to dramatically reduce the number of cases of measles, mumps and rubella infection, as well as to reduce the pain and suffering associated with each of these natural infections. Despite the undoubtable positive effects of MMR vaccination, there have been a number of recent publications that implicate the potential for debilitating serious reactions following pediatric immunization with MMR vaccine.[6-8]

The purpose of this analysis was to analyze the incidence rate of serious neurologic symptoms following primary pediatric MMR immunization of children based upon analysis of the Vaccine Adverse Event Reporting System (VAERS) database. The VAERS database is an epidemiologic database that has been maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse reactions following vaccines are to be reported to this database as mandated by US law. The CDC requires written and telephonic confirmation of all serious adverse reactions and follows up serious reactions one-year latter to determine whether or not the patient had fully recovered. We and the VAERS Working Group of the CDC, analyze and publish epidemiologic studies based upon review of the VAERS database. The VAERS working group has stated that VAERS is simple for reporters to use, flexible by design and that its data are available in a timely fashion.[9]

Materials and Methods

In this study, the VAERS database was analyzed retrospectively for serious neurologic symptoms following primary pediatric MMR immunization from 1994 through 2000 that developed within 30 days among those residing in the US. The serious neurologic adverse reactions analyzed included: cerebellar ataxia, autism, mental retardation and permanent brain damage. Descriptions of adverse reactions relied upon those reporting them and were defined by the reporting fields contained in the VAERS database. The calculated incidence rates were obtained from the estimates of the Biological Surveillance Summaries received from the CDC, and by analyzing the number of children in each year's birth cohort from 1994 through 2000 and from the CDC estimates of the percent coverage of each yearly birth cohorts with primary pediatric MMR vaccination.

The estimates indicate that 24,825,174 doses of primary MMR vaccine were administered from 1994 through 2000. Diphtheria, Tetanus and whole-cell pertussis (DTwcP) containing-vaccine serious neurologic reactions (a control) reported to VAERS from 1994 through 2000 that developed within 30 days among those residing in the US were analyzed. The CDC estimates indicate that 63,035,269 doses of DTwcP were administered from 1994 through 2000. The incidence rates of serious neurologic reactions following DTwcP vaccine recipients provided a background rate to compare against the incidence rates of serious neurologic reactions in primary pediatric MMR vaccine recipients.

A search for the incidence rate of a specific adverse reaction to one vaccine would be expected to be similar to the incidence rate following another vaccine administered to a similarly aged population; whatever the inherent limitations in the precision of reported adverse reactions to the VAERS database, they would be expected to equally affect the VAERS submissions of both vaccines under study. Similarly, the number of doses of a type of vaccine administered, based upon the CDC estimates should be unbiased. Because of the limitations in the CDC estimates, they should apply equally to each vaccine under study. The assumption of equal reactogenicity between vaccines, forms the basis of our null hypothesis.

The incidence rate of an adverse reaction following MMR vaccine in comparison to the incidence rate of an adverse reaction following the DTwcP vaccine control group determines the relative risk, attributable risk, the percent association and statistical significance of the adverse reaction for MMR vaccine. The relative risk value is obtained by dividing the incidence rate of the adverse reaction following MMR vaccine by the incidence rate of the adverse reaction following the DTwcP vaccine control group. The attributable risk value is determined by subtracting one from the relative risk. The percent association value is calculated by dividing the relative risk value by the relative risk value plus one and multiplying this computed value by 100. Statistical significance was determined by using a χ^2

2x2 contingency table, which assumed that the total number of adverse reactions following the DTwcP control vaccine and the number of doses administered for the time period examined where the expected values and the total number of adverse reactions following the primary pediatric MMR vaccine under study and the number of doses administered for the time period examined were the observed values. The statistical package contained in Corel's Quattro Pro was used and a p value of 0.05 was accepted as statistically significant.

Results

Table 1 summarizes serious neurologic symptoms reported to the VAERS database following primary pediatric MMR vaccination. The number of male and female reaction reports, mean and standard deviation of age in years, mean and standard deviation of onset in days and incidence per million MMR vaccinations were analyzed. The male/female ratios for autism (3.6) and mental retardation (2.0) indicated that these reactions occurred more predominantly in males, whereas cerebellar ataxia and permanent brain damage were fairly evenly divided between male and female vaccine recipients. The overall mean age was approximately 1.8 years-old and the mean onset time range from about 5 to 10 days following MMR immunization. Serious neurologic illnesses were reported following DTwcP vaccine as follows: 0.22 per million DTwcP vaccines for cerebellar ataxia, 0.29 per million DTwcP vaccines for autism, 0.84 per million DTwcP vaccines for mental retardation and 0.30 per million DTwcP vaccines for permanent brain damage. Table 2, summarizes the relative risk, attributable risk, percent association, statistical significance and 95% relative risk confidence intervals for serious neurologic adverse reactions reported following primary pediatric MMR vaccination in comparison to DTwcP vaccination. Cerebellar ataxia, autism, mental retardation and permanent brain damage were all statistically significantly increased following primary MMR vaccination in comparison to DTwcP vaccination.

Discussion

These results show that primary pediatric MMR vaccination in children is associated with a marked increase in serious neurologic disorders in comparison to DTwcP vaccination. The increase is statistically significant for cerebellar ataxia, autism, mental retardation and permanent brain damage following primary pediatric MMR vaccination in comparison to DTwcP vaccination. These results are remarkable considering that DTwcP vaccination has been found by the scientific and medical communities to be responsible for permanent neurologic sequellae in children.[10-13]

Previous studies have also reported on serious untoward neurological disorders following measles, mumps and MMR vaccinations. These studies noted similar temporal relationships between the onset of serious neurological disorders and vaccination, as was found in this study. Weibel et al have reported that the clustering of reactions on days eight and nine following measles-containing vaccines suggests that there is casual relationship between measles vaccine and encephalopathy.[8] In Denmark it has been reported that there were 24 reports of temporary gait disturbances after MMR vaccine.[14] The median onset following MMR vaccination was 6 days (range 3-25 days). Patient recovery occurred with a mean of 8 days (range 1-100 days), but 1 child still had gait disturbances 3 months after vaccination. Further, they observed that 8 of the 24 children had a possible cerebral disorder and 3 children seen by a pediatric neurologist were diagnosed with a cerebellar disorder and ensuing ataxia. Cerebellar ataxia has been reported after natural measles, mumps and rubella. The established rate of gait disturbances following MMR vaccine was 6 per 100,000 vaccinees. The authors reported that the symptoms usually disappeared within a few days but in some children they can last several months with cerebral involvement indicating a more severe disorder. Another study, analyzed 23 cases of neurological disorders that were reported to the CDC from January 1965 to February 1967 following 1.4 million doses of live measles vaccine.[15] The mean time of onset was 8.7 days for reactions following live measles vaccine. The incidence rate of encephalitis following live measles vaccine was 1 per 643,500 immunizations and of chronic damage was 1 per 5 million immunizations. A study conducted from 1976 to 1989 in the Federal Republic of Germany analyzed the adverse effects of approximately 5.5 million doses of vaccines containing measles, some given as monovalent vaccines, some as trivalent and some as bivalent vaccines were administered.[16] During

Table 1 - A summary of serious neurologic reactions following MMR vaccination

Type of Reaction	Number of Male Reaction Reports	Number of Female Reaction Reports	Mean Age (Years)	Mean Onset (Days)	Incidence per Million MMR Vaccines
Cerebellar Ataxia	23	21	1.4 ± 0.66	4.9 ± 4.7	1.8
Autism	29	8	1.8 ± 1.1	6.5 ± 7.2	1.5
Mental Retardation	23	12	1.9 ± 2.0	5.5 ± 6.0	1.4
Permanent Brain Damage	8	9	1.9 ± 1.2	9.7 ± 8.4	0.69

Table 2 - A comparison of serious neurologic reactions following MMR vaccination in comparison to DTwcP vaccination

Type of Reaction	Relative Risk	Attributable Risk	Percent Association	Statistical Significance	95% Relative Risk Confidence Interval
Cerebellar Ataxia	8.2	7.2	89	$p < 0.0001$	4.4 to 15
Autism	5.2	4.2	84	$p < 0.0001$	3.0 to 9.2
Mental Retardation	1.7	0.7	63	$p < 0.05$	1.1 to 2.6
Permanent Brain Damage	2.3	1.3	70	$p < 0.05$	1.2 to 4.4

this time, there were 433 spontaneous case reports of side-effects (1/12,700 doses). The most common reactions were as follows: 264 reports of fever, 159 reports of rash, 75 upper respiratory infection reports and 21 reports of conjunctivitis. These reactions occurred 7-14 days following vaccination, with 2-7 days being the next most common temporal period. There were 57 reports of parotitis between 7 days and 30 days (1 per 90,000 vaccinations), 6 reports of orchitis (1 per 1.25 million vaccinations), 11 reports of thrombocytopenia (1 per 600,000 vaccinations), 41 reports of measles seizures, all after measles-containing immunizations, 7 of these were without fever, (1 per 180,000 vaccinations), 13 reports of gait disturbances (1 per 420,000 vaccinations), 16 reports of encephalitis/meningitis (1 per 1 million vaccinations) and transient EEG changes observed in 3% of vaccinees. In a study conducted in the United States from 1963 through 1971, 84 cases of neurological disorders with onset of less than 30 days were reported after live measles virus vaccination.[17] Among these 84 cases, 76% had an onset from 6 to 15 days following immunization. The authors conclude that the clustering suggests that some may have been caused by the vaccine. The incidence rate of neurological disorders based upon this study was 1 per 1.16 million live measles vaccinations. Another study found 18 cases of neurological complications following live measles vaccine administered between 1971 to 1978 in Hamburg, Germany.[18] A causal connection was assumed by the author in 14 of the cases, resulting in an incidence of 1 per 2,500 vaccinees. The author observed an incidence of 1 per 17,650 vaccinees of abortive encephalopathy following live measles vaccination.

The pathogenesis of serious neurological reactions observed following MMR vaccination in this study and in other previous studies probably reflects the direct effects of the three live viruses present in MMR vaccine. It has been observed that patients following MMR vaccination develop many of the same symptoms as if they were infected with natural measles or mumps infections. Patients following vaccination with MMR have reported the development of rashes, fevers, gastrointestinal symptoms, gait-disturbances and neurological disorders. The overall result of the similarities between natural infection and MMR vaccination means that effects of these natural viral infections must be taken seriously as possibly occurring at a low frequency following vaccination.

It has been reported that natural exposure to live viruses can result in autism.[19,20] Another study describes some of the endoscopic and pathological characteristics of children with developmental disorders.[21] An endoscopically and histologically consistent pattern of ileocolonic pathology has been identified in a cohort of children with developmental disorders. Illeal lymphoid nodular hyperplasia was found in 54 out of 58 (93%) affected children and 5 out of 35 (14.3%) in controls ($p < 0.001$). Histologically reactive follicular hyperplasia was present in 46 out of 52 (88.5%) in affected patients and 4 out of 19 (29%) in ulcerative colitis controls ($p<0.01$). Measles virus has been associated with immunodysreglation and autism. It follows that those children vaccinated with live MMR vaccine may on rare occasions develop similar conditions.

It has recently been hypothesized that by combining the three live viral components of MMR vaccine that there is an increased severity of adverse reactions following MMR vaccination then would be expected based upon the reactogenicity profiles of each of the component vaccines of MMR vaccine administered individually.[7] We have analyzed other studies that have examined the reactivity of individual components of MMR and combined MMR vaccines, and found this to be true. A Japanese study analyzed the incidence rate of meningitis following mumps vaccine and MMR vaccine.[22] They found that in laboratory-confirmed mumps vaccine-related meningitis patients developed an increased relative risk following MMR vaccine in comparison to mumps vaccine as follows: fever (relative risk = 4.1), vomiting (relative risk = 4.8), headache (relative risk = 2.0), meningeal irritation signs (relative risk = 4.8), convulsions (relative risk = 7.5) and parotid swelling (relative risk = 2.0). They also reported a statistically significant difference in the time interval from vaccination to the onset of meningitis following MMR vaccine in comparison mumps vaccine. Our review of a British study, revealed that there was an increased relative risk in the incidence rate of fever (relative risk = 1.1), rash (relative risk = 1.6) and off-food (relative risk = 1.4) adverse reactions following MMR vaccine in comparison to measles vaccine.[23]

In order to alleviate many of the difficulties encountered with the MMR vaccine, we suggest that a killed MMR vaccine should be made available as it may reduce the number and severity of adverse reactions following live MMR vaccine. A study conducted in England by the British Medical Research Council, compared the safety and efficacy of a killed measles vaccine followed by a live measles vaccine against that of a live measles vaccine.[24] This study involved about 10,000 children vaccinated with a killed measles vaccine followed by a live measles vaccine, 10,000 children vaccinated with live measles vaccine, and 16,000 children who were not vaccinated. The efficacy portion of this study showed that those vaccinated with the combination of a killed measles vaccine followed by a live measles vaccine developed measles at a rate of only 12 per 1,000 children six months following vaccination, whereas those vaccinated with the live measles vaccine developed measles at a rate of 16 per 1,000 children and those that went unvaccinated developed measles at a rate of 94 per 1,000 children. The safety portion of the study showed that seizures reported following 21 days vaccination occurred randomly following killed measles vaccine followed by live measles vaccine at an incidence rate of 0.7 per 1,000 children, whereas they occurred non-randomly (peak from 6-9 days) following live measles vaccine at an incidence rate of 1.9 per 1,000 children. The incidence of seizures in the unvaccinated group was 0.3 per 1,000 children. Additionally, there were marked decreases in the incidence of vomiting, malaise, rash and fever following killed measles vaccine followed by live measles vaccine in comparison live measles vaccine. The killed measles vaccine used in this study was manufactured by Pfizer Ltd. We also suggest that if the current live MMR vaccine is to remain in use that parents should have the option to have each of the components of MMR vaccine administered individually at different times.

In conclusion, this study showed a highly statistically significant increase in serious neurologic conditions following primary pediatric MMR vaccination in comparison to a DTwcP vaccine control group. This finding confirms and extends a number of previous studies showing that patients are at increased risk for developing serious neurologic disorders for about 5-10 days following pediatric MMR vaccination. The pathogenesis of these reactions appears to follow a similar course as in the natural viral infections. In order to alleviate the potential for serious neurologic disorders following primary pediatric MMR vaccination, we recommend that killed MMR vaccine be made available. If live MMR vaccine is to be used, parents should have the option to have each viral component of MMR vaccine administered separately.

Those children who develop sequella following MMR vaccine should report their reactions to the VAERS database and should also apply for compensation under the no-fault Vaccine Compensation Act. The VAERS program can by reached 24 hours a day at 1-800-822-7967 and the Vaccine Compensation Act can be reached at 1-800-338-2382. It is clear that with the potentially globally destructive effects of natural measles, mumps and rubella infections that continued vaccination is necessary, but improvements in MMR vaccine is needed to improve its safety.

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