Measles, Mumps, Rubella (MMR) Vaccine

A. P. Dubey and S. Banerjee

Department of Pediatrics, Maulana Azad Medical College, New Delhi, India.

Abstract. MMR is a live attenuated vaccine. Indian children show almost 90% seroconversion against measles and rubella and 90% against mumps. Several adverse effects have been reported. Epidemiological studies do not support a causative link between MMR and autism, IBD or GBS. There is an association between the Urabe strain of mumps vaccine and viral meningitis. Vaccine associated thrombocytopenia has been reported. Severe hypersensitivity reactions occur, mainly due to the gelatin component. Outbreaks of measles occur in areas of high measles vaccine coverage, when susceptible individuals accumulate. A second dose is given mainly to vaccinate those who missed the first dose or had primary vaccine failure, rather than to boost waning antibody levels. The possibility or eradication of mumps with a second dose of mumps vaccine is being considered. [Indian J Pediatr 2003; (7) : 579-584] E-mail : apdubey52@rediffmail.com

Key words : MMR vaccine; Immunization; Controversies; Adverse effects

Measles, Mumps, Rubella (MMR) vaccine provides protection against all the three diseases. Live attenuated measles and rubella vaccines were developed independently of each other, and they have proven to be extremely effective in preventing the transmission of these viruses. In 1971, measles and rubella vaccines were combined with a live attenuated mumps vaccine and approved for use in the United States as the trivalent MMR. This formulation has become the dominant method of immunization in developed countries, although individual vaccinations still occur in underdeveloped countries. In India, this vaccine is manufactured by the Serum Institute of India Ltd, at Pune. The respective strains used are Edmonston Zagreb for measles, L- Zagreb for mumps and Plotkins RA27/3 for rubella. The measles and rubella components are produced using human diploid cells. The mumps vaccine is produced from chick embryo cells. The individual harvests collected from the infected cells are pooled and blended in such a way that will yield a virus concentration of measles virus not less than 1000 TCID50, mumps virus not less than 5000 TCID50 and rubella virus not less than 1000 TCID50. The combined MMR vaccine yields results similar to administering individual measles, mumps, and rubella vaccines at different sites.

MMR is a safe vaccine with high levels of immunogenicity and low levels of reactogenicity. A number of epidemiological studies have demonstrated the effectiveness of the vaccine by adequate seroconversion and a significant reduction in the incidence of the three target diseases. Studies in Indian children using indigenously produced vaccine have shown almost total seroconversion against measles and rubella and 90% seroconversion against mumps.1

CONTROVERSIES REGARDING SIDE EFFECTS

Untoward effects following active immunization have been reported with all vaccines. All such reports should be evaluated thoroughly, and if warranted, the current vaccination policy should be changed. If no evidence of a causal relation can be found, the public must be informed of the confirmed safety and continuing importance of the immunization. This is a prerequisite for maintenance of sufficient vaccination coverage, which is especially important in the prevention of such highly infectious diseases as measles.

During recent years, public concern has been caused by the attribution of causation of several disorders, including Autistic spectrum disorders (ASD), meningitis, inflammatory bowel disease, and Guillain Barre Syndrome (GBS) to MMR vaccination. As a result of the concern surrounding the MMR vaccine, there was a documented decrease in immunization rates in the United Kingdom and Ireland. This led to an upsurge in the annual rates of measles infection.2

MMR VACCINE AND AUTISTIC SPECTRUM DISORDERS

In 1998, investigators published a report on 12 children referred to a London pediatric gastroenterology unit, for the evaluation of gastrointestinal diseases associated with developmental regression.3 The parents of eight of these children associated the onset of behavioral symptoms with administration of MMR vaccine. It was hypothesized that maternal immunization with MMR before, during, or after pregnancy predisposed the child to autism.4 Another proposal put forth was that genetically at-risk children might be predisposed to autism by a G-alpha protein defect. It was hypothesised
that live measles vaccine depleted body stores of vitamin A, resulting in metabolic and immunologic changes and precipitating behavioral changes in children with ASD. Hence it was felt that supplementation with natural forms of vitamin A would improve the symptoms of ASD.

Subsequently, a detailed study in the United Kingdom using the case-series method revealed that there was no temporal relationship between MMR immunization and development of autism. This study found no clustering of cases of developmental regression in the 2-4 month period after MMR immunization, no temporal association between ASD and MMR vaccine (over a 6-month interval), and no increase in the rate of reported ASD associated with the introduction of MMR vaccine. However, the appropriateness of using the case series method for detecting associations between vaccines and chronic diseases, which often have variable times of onset after exposure, was questioned by certain authors. Another report using data from the United Kingdom general practice research database found a nearly fourfold increase in the incidence of autism among 2-5-year-old boys born between 1988 and 1993. However, during the same time period the prevalence of MMR immunization rates remained constant (95%). Hence it was concluded that the increased rate of reporting of ASD was not affected by the introduction of MMR vaccine in the United Kingdom.

Similarly, the California Department of Health observed that there were only small increases in the percentage of children who had received MMR by 24 months of age during 1980 to 1987, while there was an almost six-fold increase in the number of children with ASD during the same period. Another set of investigators found no vaccine-associated cases of inflammatory bowel disease or autism in 1.8 million Finnish children who received almost 3 million doses of MMR vaccine over a period of 14 years.

Finding a temporal association in a selected population for a disorder with wide individual variation in timing of onset, provides weak evidence for an association, especially since the broad age range for recognized onset of symptoms of ASD overlaps with the age when MMR vaccine is routinely administered. Thus, some temporal associations are expected. Increased reporting of ASD in recent years does not correlate with the introduction and widespread use of MMR vaccine. Furthermore, no temporal clustering of reported onset of ASD symptoms has been noted. If measles or MMR vaccines were associated with an increased risk of ASD in the weeks or months after immunization, a temporal clustering in the time of onset after immunization should be identifiable. Changes in behavior have been reported to occur as early as 1 day and as long as several months after MMR vaccine administration. Thus, there is temporal ambiguity in the timing of reports of behavioral symptoms after immunization. The inherent heterogeneity in the timing of onset of the manifestations of ASD, the probable variability in expression of genetic predisposition, and the known variability in the ultimate manifestations could possibly contribute to this temporal ambiguity.

Measles vaccines were introduced in the United States in 1963. In 1989, a second dose was recommended at 4 to 6 years of age or 11 to 12 years of age, which is well after the usual age of onset for ASD. There have been no reports of late-onset ASD associated with the receipt of this extra dose of measles or MMR vaccines.

Studies were conducted by the Institute of Medicine in the USA and the Medical Research Council in the UK. Their conclusions were that although the epidemiological studies so far do not support a link between MMR and autism, they have been too imprecise to rule out the prospect completely and there is need for further research.

MMR VACCINE AND INFLAMMATORY BOWEL DISEASE (IBD)

Some authors have proposed an epidemiological association between IBD and either measles, measles vaccine or MMR vaccine. It was hypothesised that measles caused IBD due to the following reasons: (1) Measles nucleocapsid antigen was found in the intestinal wall of patients with IBD by immunohistochemical staining and PCR assay for measles genomic RNA. (2) Wild type measles virus was found in the peripheral blood monocytes in a few patients of Crohn's disease. (3) Higher concentrations of serum measles IgM were detected in some patients with IBD.

Montgomery et al prospectively studied a cohort of persons born during 1970 in the United Kingdom. None of the individual childhood infections were significantly associated with IBD, however a significant association was found for having had measles and another infection in the same year during the first 6 years of life. If measles was not one of multiple infections in a year or if mumps was not included as a second infection, the association disappeared. The authors noted that mumps before 2 years of age seemed to be associated with ulcerative colitis and suggested that, atypical patterns of exposure might be a risk factor for IBD. In this sample, only 4% of the entire population experienced this pattern of exposure. There are several limitations in this study. First, the association between measles and mumps in the same year and IBD was one of many associations examined, and a finding of significance attributable to chance cannot be ruled out. Second, parental histories were obtained 4 to 10 years after reported infections occurred, and estimation of approximate ages at the time of infections could have resulted in artificial clustering by age. Third, the number of studied persons with IBD was small. Fourth, a history of 2 wild-type par myocardiovirus infections during the same year is not comparable immunologically to simultaneous immunization with attenuated virus vaccines. No associations between measles or mumps and IBD were