Review Article

Current Recommendations on MMRV combination vaccine in India

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Abstract

Two MMRV vaccines have been available since 2000. ProQuad (Merck & Co., Inc, West Point, PA; Merck) and Priorix-Tetra (GlaxoSmithKline Biologicals, Rixensart, Belgium; GSK). Both have been widely used in USA, Australia, Canada, and many European countries. The MMRV vaccine was developed based on the existing MMR and varicella vaccines [1,2]. Licensed ProQuad and Priorix-Tetra have different measles virus strains (Edmonston strain and Schwarz strain, respectively) with the same titer ($\geq 10^{3.0}$ tissue culture 50% infective dose, TCID50). Mumps virus strain in Priorix-Tetra (RIT 4385 strain, titer $\geq 10^{4.4}$ TCID50) is derived from what is used in ProQuad (Jeryl Lynn strain, titer $\geq 10^{4.3}$ TCID50). ProQuad and Priorix-Tetra have same rubella virus strain (Wistar RA 27/3 strain) and titer ($\geq 10^{3.0}$ TCID50). They also have same varicella virus strain (Oka strain), but with different titers ($\geq 10^{3.99}$ and $\geq 10^{3.3}$ plaque-forming units, respectively).

Keywords: Immunization, MMRV vaccine, Immunogenicity, Seroconversion rate, Advisory Committee on Immunization Practices (ACIP).

Introduction

Advisory Committee on Immunization Practices (ACIP) recommended in 2010 about MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. First dose is advised at 12 -15 months and second dose either 3 or more months after first dose or at > 48 months of age. For the first dose in 12 – 47 months of age, either MMR + varicella (V) (both are given in same sitting but separately) or MMRV vaccine may be used. Parents and guardians should be counselled about benefits and risks of both vaccination options. MMR +V should be given as first dose in this age group unless parents and guardians clearly opt for MMRV after counselling of higher risk of fever, rash and febrile seizures with first dose of MMRV. For the second dose at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine is preferred over MMR+V[1-3]. IAP ACVIP recommends that the varicella vaccine be given separately as MMR+V (varicella) at 15 months age and either the same (MMR+V) or MMRV be offered at 4-6 years of age. For catch up vaccination of children more than 48 months age, if both MMR and varicella vaccines not given earlier; two doses of MMRV or MMR + V separately be given 6 weeks to 3 months apart[4].Combination vaccines are generally preferred over multiple single antigen vaccines due to many reasons. Similar was the experience of a german study when MMRV was replaced by MMR+V[5,6]. As vaccination coverage improve when vaccines are given at earlier age and in combination of multiple antigens, seroconversion, long term vaccine efficacy and safety issues were studied when MMRV was given at earlier age.

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Immunogenicity studies

Immunogenicity and non inferiority phase III study by GSK evaluating effect of MMRV/ MMRV (PRIORIX-TETRA) vaccine compared to two doses of MMR+V /MMR (PRIORIX) and (VARILRIX). The study continued for 3 years evaluating the persistence of antibodies of each of the vaccine antigens in 11-23 months. The study show similar and high seroconversion in two groups. Following Dose one in each MMRV and MMR+V groups seroconversion rates were 99%, 85.7%, 100%, 100% and 100%, 95.3%, 100%,100% for measles, mumps, rubella and varicella respectively. Similar values after dose 2 were 100%, 100%, 100%, 100% and 100%, 99.1%, 100%,100% respectively. Antibody level after 3 years of follow up show similar pattern and also no

breakthrough cases[7]. Seropositivity rates to measles, mumps and rubella in children15-23 months and 24-72 months of age were similar in MMRV and MMR+V in another study[8].. Studies in Europe showed 1.83 times higher GMT (4828 versus 2633) for measles 1.06 times higher GMT for mumps (1564 versus 1465), comparable for rubella (120 versus 130) and 27 times higher GMT for Varicella (2587 versus 95) seroconversion for MMRV versus MMR+V in children vaccinated of age group of 11-23 months[9]. Ten RCTs with 8961 healthy children with MMRV and MMR+V vaccines showed comparable immunogenicity against measles (relative risk [RR] = 0.99, 95% CI = 0.98–1.00), mumps (RR = 0.99, 95% CI = 0.97–1.00), rubella (RR = 1.00, 95% CI = 1.00–1.01) and varicella (RR = 0.98, 95% CI = 0.95–1.01). At least 93% of children in both groups had seroconverted within 6 weeks. The immunogenicity of MMRV and MMR+V vaccines was comparable in healthy children[10].Indian study performed in Goa, Chennai, Bangalore, Kolkata and Pune with subjects of 9 to 15 months dividing into three groups. Group 1 received MMRV/MMRV, Group 2 received MMR/ MMRV and Group3 received MMR/MMR+V. All three groups showed 100% seroconversion post dose 2 for all the four antigens. Antibody level analysis showed higher GMT in MMRV groups for measles (4471 versus 3358 versus 2495), for mumps (6428 versus 10108 versus 4925) and for rubella (148 versus 164 versus 173) and varicella (5318 versus 198 versus 128) than MMR/MMRV or MMR/MMR+V. This shows very high antibody levels attained in lower ages with MMRV[10,11]. For immunogenicity, many RCTs suggested that single MMRV dose in healthy children aged 9 to 24 months had comparable immunogenicity profiles against these 4 diseases to MMR + V/MMR. There are some exceptions as follows[12].

1. Anti measles GMT was significantly higher in MMRV group than that in MMR+V/MMR group, the GMT ratios were 1.66 (95% CI 1.48, 1.86; P < 0.001) and 1.62 (95% CI 1.51, 1.70; P<0.001), respectively.
2. Pooled seroconversion rate for mumps in MMRV group was significantly lower by 2% to 6% than those in MMR + V group (RR = 0.98; 95% CI 0.95, 1.00; P = 0.020) and MMR group (RR = 0.94; 95% CI 0.90, 0.99; P = 0.017). The slight lower seroconversion rate for mumps might partly be due to the lower mumps virus titer in the early experimental formulation of MMRV, which led to inclusion of a higher viral titer of mumps component in the final licensed formulation.
3. Anti rubella GMT was lower in MMRV group than that in MMR + V/MMR group, with the GMT ratios of 0.81 (95% CI 0.78, 0.85; P < 0.001) and 0.79 (95% CI 0.76, 0.83; P < 0.001), respectively. This reflected an about 20% lower post vaccination anti rubella GMT after MMRV. Considering the same rubella virus strains and equal virus titres in MMRV and MMR, potency of rubella virus in MMRV might be weakened by the existence of varicella virus.

Long term vaccine efficacy studies

Three year follow up study show persistence of seropositivity rate in MMRV/MMRV versus MMR+V to 99% versus 97% for measles. Similar figure for mumps, rubella and varicella were 97.4% versus 93.8%, 100% and 99.4% and 96.8% respectively[13]. Another 10-year follow-up study reported a high 2-dose monovalent varicella vaccine efficacy of 94.4% to 98.3% in healthy children aged 1-12 years given 2 doses 3 months apart[14]. Considering the fact that longer term efficacy data are limited for MMRV and immunogenicity of Monovalent or MMRV are comparable it can be assumed as of now similar long term efficacy with 3 month apart 2 doses schedule.

Safety studies

A meta analysis of 10 RCTs with 8961 healthy children with MMRV and MMR+V vaccines showed significantly higher incidences of fever (RR = 1.19, 95% CI = 1.09–1.31) and rash (RR = 1.23, 95% CI = 1.06–1.43) in MMRV group[15]. Single MMRV dose in healthy children aged 9 to 24 months is generally well tolerated. Significant differences were found mainly in the comparisons of fever and rash. Fever was the most frequently reported symptom during the 43 days (days 0 – 42) of follow up period and were above 52.9% . Higher incidences of fever were found in MMRV as compared to MMR + V and MMR (RR ranged from 1.12 to 1.60). Rash was the second frequently reported symptom. Generalized rash (RR = 1.23; 95% CI 1.07, 1.40; P = 0.004) and measles/rubella like rash (RR =1.44; 95% CI 1.15, 1.81; P = 0.002) were significantly more frequent in MMRV than in MMR + V. Moreover, measles/rubella-like rash (RR = 1.45; 95% CI 1.06, 1.98; P = 0.020) and varicella-like rash (RR = 1.95; 95% CI 1.04, 3.66; P = 0.040) were significantly more frequent in MMRV than in MMR[12]. The results were consistent with a statistical modelling in a previous review, which indicated that the higher level of measles antibody titre after receipt of MMRV was positively associated with the higher rates of fever and measles-like rashes[16].The higher fever rate made the incidence of febrile seizure be more concerned. In several post marketing observational safety surveillance studies, an approximate 2-fold increase in risk for febrile seizure during 7 to 10 days or 5 to 12 days after vaccination were found among children aged 10 to 24 months, those who received the first dose of MMRV compared with those who received the first dose of MMR administered with or without varicella vaccine[17-21]. Comparing serious adverse events (SAEs) between single dose MMRV and MMR+V/MMR, incidences were around 1% in all the groups; only about one-tenth of the events were considered to be related to vaccination studied. About half of the related SAEs were febrile seizures. The incidence of related febrile seizure was under 0.8% in MMRV groups and under 0.5% in MMR + V/MMR groups. No statistical difference was found between groups with no evidence of heterogeneity. No related fatal SAE was reported in any studies included[12]

Pooled analysis of 3 European studies were done to compare fever incidence in 2 weeks post vaccination period following MMRV (N= 2206) and MMR+V (N = 574) given as MCV1. Both fever of any grade and grade 3 were more common in children administered MMRV than MMR+V (61.15% versus 45.82%) and (11.20% versus 7.49%) (p < 0.05) respectively[9]. Controlled clinical trials suggest that fever rates (any grade as well as grade 3) are comparable following the MMRV vaccine (vs. MMR vaccine or MMR+V vaccine) as MCV2 in 12 -- 24 months children. This includes studies with 2 doses of MMRV or MMR followed by MMRV. Incidence of any fever ranged from 25% -- 40% and high fever (grade 3) from 2% -- 6% in MMRV group and figures for MMR+V group were 20% -- 50% and 2.5% -- 5.7% [22-25].A post-licensure study in Germany for febrile convulsion incidence was compared following MMRV 1st dose at 11 –14 months and 2nd dose at 15 – 23 months found increased risk with 1st dose of MMRV vaccine given as 1st dose of MCV[21-25]. Adjusted odds ratio for febrile convulsion during main risk period (5-12 days following vaccination) with MMRV vs. MMR or MMR+V showed one additional febrile convulsion was seen per 2747 vaccinations with MMRV (in comparison to MMR/MMR+V). The German study suggested that elevated risk of febrile convulsion is not seen when MMRV vaccine was given as MCV2[26-29]. We analyzed a recent Indian study for fever and Febrile convulsion in Indian children following MMRV. Participants were randomized (2:2:1) to receive 2 doses of either MMRV (MMRV/MMRV group) or MMR followed by MMRV (MMR/MMRV group) or MMR followed by MMR+V (MMR/MMR+ V, control group) at 9 and 15 months of age[11]. Fever rates were comparable for amongst children who received MMR vaccine or MMRV vaccine for MCV1 (Table 1) and MMRV or MMR+V for MCV2 (Table 2). No cases of febrile convulsions were reported in 15 day risk period. Although this may be related to the epidemiological context in India, which differs from developed countries, the reason is unclear. In general, the reporting rate of fever was also lower than that seen in other studies. Again, this may be due to the younger age of children

enrolled, or the presence of maternal antibodies, which may have limited measles virus replication post dose 1, resulting in the blunting of immune response and fever response rates; or differences in the reporting of symptoms. Further data may be needed to determine if there is in fact a difference in the reactogenicity profile between developed and developing countries. Three RCTs suggested that MMRV vaccine seemed to be more immunogenic and well tolerated when given as a second dose after MMR in children aged 15 months to 6 years and two RCTs suggested that MMRV vaccine seemed to be more immunogenic and well tolerated when given as a second dose after MMR + V vaccination in children aged 15 months to 6 years[30]

Table 1: Fever rate in 0-15 days following dose 1

	Vaccine at Dose 1 (No. of subjects)	Fever (any grade) % (95% CI)	Fever (high grade) % (95% CI)
MMRV/MMRV	MMRV [n=174]	32.2 (25.3 to 39.7)	3.4 (1.3 to 7.4)
MMR/MMRV	MMR [n=172]	28.5 (21.9 to 35.9)	1.7 (0.4 to 5.0)
MMR/MMR+V	MMR (n=84)	21.7 (13.4 to 32.1)	1.2 (0.0 to 6.5)

Table 2: Fever rate in 0-15 days following dose 2

	Vaccine at Dose 2 (No. of subjects)	Fever (any grade) % (95% CI)	Fever (high grade) % (95% CI)
MMRV/MMRV	MMRV [n=155]	17.4 (11.8 to 24.3)	1.3 (0.2 to 4.6)
MMR/MMRV	MMR [n=159]	28.5 (8.4 to 19.5)	1.3 (0.2 to 4.5)
MMR/MMR+V	MMR (n=79)	21.7 (8.1 to 25.0)	0.0 (0.0 to 4.6)

MMRV vaccine may be administered simultaneously with other vaccines recommended for children aged 12–15 months and 4–6 years. If simultaneous administration is not possible, MMRV vaccine may be administered at any time before or after an inactivated vaccine but at least 28 days before or after another live, attenuated vaccine, except varicella vaccine, for which a minimum interval of 3 months is recommended[3]

Schedules of vaccination:Throughout the globe MMRV is now used at lower age. In USA ACIP recommends in age12– 47 months either MMRV or MMR+V may be used but MMR+V are preferred for the first dose and for second dose in age 15 months – 12 years MMRV is preferred due to increased risk ok of febrile seizure in < 47 months children with first dose of measles containing vaccine. In Canada recommendations on MMR are same as ACIP. In Germany MMR+V is given in 11-- 14 months of age and in 15 – 23 months either MMR+V or MMRV are recommended[30-32].Australian national immunization program recommends that MMRV vaccine 18 month schedule point is a new requirement. MMRV vaccine must NOT be administered as the first dose of MMR-containing vaccine in children less than four years of age. There is a small increased risk of fever when MMRV vaccine is given as the first MMR-containing vaccine dose in this age group, compared to administering the MMR and varicella vaccines separately. Overall, the risk of fever, and the subsequent risk of febrile convulsion in children is greatly reduced by having a schedule with the first vaccine dose as MMR at 12 months and the second vaccine dose as MMRV at 18 months. MMRV is not recommended in children 14 years of age or older due to a lack of data on safety and immunogenicity/efficacy in this age group[33].

IAP ACVIP Considerations

IAP ACVIP analyzed data available at present and also considered that:

- MMR vaccination schedule endorsed by IAP of three doses at 9 months, 15 months and 4-6 years. Combination vaccines lead to more compliance in vaccination.
- Varicella vaccine may be given two doses at 3-6 month apart with first dose at 15 month[34].
- Earlier age MMRV and MMRV as MCV2 is immunogenic and safe.
- MMRV as MCV1 in 12-23 months children show increased incidence of Fever, Rash and Febrile convulsion

So, we may recommend

- MMRV1 at 15 months following MMR at 9 months of age
- MMRV2 may be given after discussing with the parents and caregivers that chance of breakthrough infection is almost abolished with a dose 3-6 months after MMRV1 and preferred.

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