DRUG REVIEW

A New Combined Vaccine Against Measles, Mumps, Rubella and Varicella in India

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A quadrivalent MMRV (measles-mumps-rubella-varicella) combination vaccine has recently been launched in India. This vaccine is highly immunogenic, with seroconversion rates against all antigens reaching 96.6-100% at 42 to 56 days after the second vaccine dose in unvaccinated children or in those previously vaccinated with MMR+/-V. Two doses efficacy, against all varicella is 94.1% and effectiveness reaches 91%. The most frequent solicited local adverse event after MMRV vaccine is redness, and fever is the most common solicited general symptom. Higher rates of fever and febrile convulsions compared to MMR+/-V have been reported when used as first dose but not when used as the second of a measles containing vaccine, irrespective of age of the second dose.

Keywords: *Chicken pox, Measles-Mumps-Rubella vaccine, Prevention, Varicella*

Measles, mumps, rubella and varicella are vaccine-preventable diseases with the potential for significant morbidity and even mortality [1-4]. Monovalent measles, mumps and rubella vaccines were introduced in the 1960's, with the first combined measles-mumps-rubella (MMR) vaccine launched in the USA in 1971 [5]. Measles vaccine was introduced in Indian Universal Immunization Programme (UIP) in 1985, and following the adoption of the global measles and rubella strategic plan, it was recommended that rubella-containing 'MR' vaccine should replace monovalent measles vaccine for the first and second measles-containing vaccine (MCV) doses [6]. However, the Indian Academy of Pediatrics (IAP) recommends a three dose MMR schedule at 9 months, 15 months and 4-6 years [7].

Although first licensed in Germany in 1984, the varicella vaccine is still not globally implemented in national immunization programs. In India, the IAP recommends varicella dose 1 at 15 months followed by dose 2 between 4-6 years of age [7]. Alternatively, the second varicella dose can be administered below four years of age provided that more than 3 months have elapsed since the first dose [7]. Varicella vaccination can be delivered either by monovalent varicella (V) or quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines [4]. There are several potential advantages of using combination vaccines [8-11]. The number of vaccination visits and administrations (pricks) can be reduced, thereby increasing vaccination acceptability, promoting compliance and improving coverage rates [9-11]. Combination vaccines simplify and shorten the reconstitution process and require less storage space than single or low valency vaccines.

Although being globally available for over ten years, MMRV has only recently been introduced in the Indian market [12]. This review evaluates the clinical evidence for efficiency and safety of this combination vaccine.

The Combined MMRV Vaccine

Priorix-Tetra (GSK, Belgium) was developed based on the existing MMR (Priorix, GSK, Belgium) and varicella vaccines (Varilrix, GSK, Belgium) [11]. Priorix-Tetra comprises a lyophilized powder containing live, attenuated measles (Schwarz strain; $\geq 10^{3.0}$ $CCID_{50}$), mumps (RIT 4385 strain; $\geq 10^{4.4}$ $CCID_{50}$), rubella (Wistar RA 27/3 strain; $\geq 10^{3.0}$ $CCID_{50}$) and varicella (Oka strain; $\geq 10^{3.3}$ PFU) viruses [11]. It is indicated in children aged 1 to 12 years to protect against measles, mumps, rubella and varicella [12]. In India, the vaccine is reconstituted with the supplied diluent before subcutaneous or intra-muscular administration [12].

Immunogenicity

Immunogenicity has been assessed in randomized controlled multi-national trials involving over 3000 children (***Web Table* I**) [13-20]. Studies evaluated either two MMRV doses, or a single MMRV dose after MMR with/without varicella.

Two MMRV doses in the second year of life compared with MMR+V followed by MMR

In the first, open, randomized controlled multicenter study conducted in Germany, 970 healthy, MCV unprimed toddlers aged 10-21 months received either two MMRV doses, or separately administered MMR+V followed by MMR; both doses were separated by 42 days [14]. At 42 days post-dose 2, seroconversion rates against all antigens were ≥98.3% (MMRV group) and ≥97.5% (MMR+V group). At this time point, the geometric mean titres (GMT) for measles and mumps in the MMRV group were significantly higher than in the MMR+V group. The rubella GMTs were not significantly different between the groups, and as expected, the varicella GMTs were significantly higher in MMRV recipients than in those who did not receive a second varicella dose [14]. In another open, randomized controlled multicenter study, from Austria and Germany, 494 healthy toddlers aged 12-18 months received either two MMRV doses, or MMR+V followed by MMR, both doses were separated by 42-56 days [15]. All subjects in both groups seroconverted for measles, rubella and varicella post-dose 2; 98.0% (MMRV) and 99.1% (MMR+V) seroconverted for mumps. Measles and varicella GMTs were significantly higher in the MMRV group [15]. Three years post-dose 2, antibodies against the vaccine antigens persisted after both MMRV (≥97.4%) and MMR+V (≥93.8%), and all subjects remained seropositive to rubella [16].

MMRV as second dose of MMR vaccine

Healthy children aged 15-75 months primed with single-dose MMR+V ≥6 weeks previously, received a second dose of either MMRV or MMR+V in a randomized open multicenter study in 390 children from Italy and Canada. All MMRV subjects seroconverted against all four diseases (***Web Table* I**) [17]. Similar increases in GMTs from pre- to 42 days post-dose 2 occurred in both groups for all antigens, but were particularly marked for varicella. In another multicenter study, from France, Germany and Italy, MMR-primed children received a second dose of MMRV or MMR+V, either at 15 months–2 years or 2-6 years (***Web Table* I**) [18]. All subjects were subsequently vaccinated 42-56 days later with a single dose of monovalent V. After the second dose of either MCV, ≥98.9% subjects in both age groups had seroconverted against measles, mumps and rubella. After one V dose, ≥96.6% subjects had seroconverted; this increased to 100% after the second V dose [18].

Immunogenicity in Indian children

A phase III open randomized study undertaken at six tertiary care centers in India administered either two doses of MMRV, MMR followed by MMRV, or MMR followed by MMR+V (control) to children aged 9-10 and 15 months [19]. After 43 days of MCV dose 2, 100% seropositivity was recorded for MMR antigens in the MMRV/MMRV and MMR/MMRV arms, and varicella in the MMRV/MMRV arm (***Web Table* I**). Seroconversion rates in the MMRV/MMRV and MMR/MMRV arms were non-inferior to the controls. Multi-fold increases in GMTs were seen for all antigens from 43 days post-dose 1 to 43 days post-dose 2, particularly with respect to varicella [19].

Efficacy and effectiveness studies

Two doses of either MMRV or MMR (control), or single-dose MMR followed by MMR+V (both doses separated by 42 days) were compared in a large European multicenter study of 5803 children (aged 12-22 months; mean 14.2 months) [20]. After 3-years of follow-up, varicella cases were confirmed in 37/2279 (MMRV), 243/2263 (MMR+V) and 201/743 (MMR) subjects, of which 2, 37 and 117, respectively were moderate-to-severe. The efficacy of two-dose MMRV was 94.9% against all varicella and 99.5% against moderate-to-severe varicella compared with 65.4% and 90.7%, respectively after MMR/MMR+V (i.e., single-dose V). The authors concluded that two-dose varicella vaccine administered with a short interval provided the optimum protection against the disease [20].

Efficacy until ≥6 years post-vaccination has recently been demonstrated following two-dose MMRV (95.0% (all varicella) and 99.0% (moderate-to-severe varicella), compared with 66.9% and 90.2%, respectively after single-dose V) [21].

The effectiveness of MMRV and V vaccines was assessed in 1084 children during seven varicella outbreaks in day-care centers in Germany. The overall vaccine efficacy (71% in 352 eligible children, $P<0.001$) was particularly sensitive to disease severity and number of vaccine doses. The effectiveness of two-dose MMRV vaccine against any varicella disease was 91% ($P=0.001$) [22].

SAFETY

Several reviews have concluded that MMRV and MMR+V have comparable safety profiles [10,23]. A pooled analysis of three large trials demonstrated that within four days of doses 1 and 2, redness followed by swelling and pain were the most frequent solicited local symptoms after MMRV, MMR+V and MMR vaccines, (***Fig.* 1**) [11]. During the first 15 and 43 days post-vaccination, fever was the most common solicited

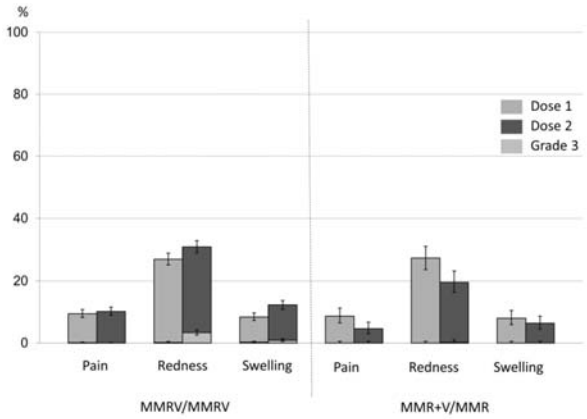

FIG. 1 *Pooled analysis of incidence of solicited local adverse events within 4 days of administration of two MCV doses. (created using data provided in reference 11)*

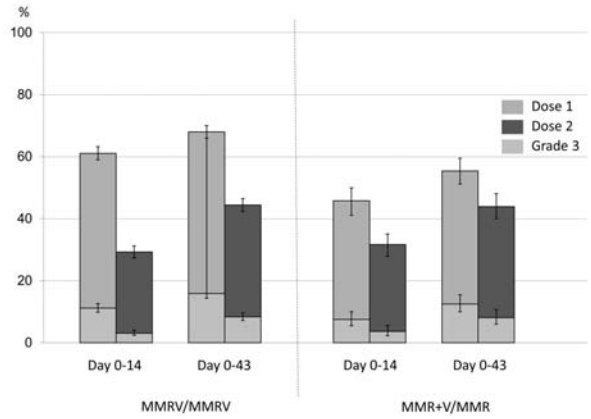

FIG. 2 *Pooled analysis of incidence of fever within 14 and 43 days of administration of two MCV doses. (created using data provided in reference 11)*

general symptom after all MCV doses [14,15]; although, the incidence decreased after the second dose (***Fig.* 2**) [11]. In the two largest European studies, rectal temperatures ≥38.0°C were more frequent after MMRV than MMR+V for 15 days post-dose 1 [(59.8% *vs* 51.3%; *P*=0.023) [14] and (67.7% *vs* 48.8%; *P*<0.05) [15]]. Unsolicited adverse events up to 43 days after vaccination did not differ between the vaccine groups. In the largest trial, these were reported in 45.4% and 43.3% after MMRV and MMR+V post-dose 1 and 41.1% and 30.9%, respectively post-dose 2; these differences were not statistically significant [14].

'Any' rash occurs in 10.8-19.6% subjects during 43 days post-MMRV vaccination [10]. However, the incidence of measles, rubella or varicella-like rashes, which are actively followed in clinical trials, is generally low and not significantly different after MMRV or MMR+V [11].

In the early trials, vaccine-related febrile convulsions were recorded in one (out of 732) and two (out of 371) subjects post-MMRV dose 1 [14,15]. In a German study of 226,267 MCV-unprimed children aged <5 years (90% aged between 11-23 months) vaccinated with a first dose of MMR (*n*=111,241), MMR+V (*n*=32,370) or MMRV (*n*=82,656), based on the "FC Jacobsen" definition, the adjusted odds ratio (95% CI) for hospitalization with febrile convulsion after the first MMRV dose (vs. MMR/MMR+V) during the main risk period (5-12 days) was 2.4 [95% CI 1.5-4.0]. The risk of FC compared to MMR/MMR+V was estimated as one additional seizure for every 2,747 vaccinated subjects [24].

Controlled trials have not indicated an increased risk of fever after a second MMRV dose. The frequency of fever (≥38.0°C) post-dose 2 tends to be lower than post-dose 1 (***Fig.* 1** and ***Table* I**); the incidence of fever after MMRV is also no different than MMR+V [(36.8% *vs* 33.1%) [14]; (43.1% *vs*. 47.5%) [15]; ***Table* I**]. Results of a post-licensure study in German children (MMR 98,348; MMR+V 10,315; MMRV 50,350 participants) suggest no statistically significant increase of febrile convulsion after the second MMRV dose (compared to MMR or MMR+V), even when administered in the second year [25].

Safety in Indian children

In the phase III study in Indian children, pain was the most common local symptom after the first vaccine dose (MMRV/MMRV 11.5%; MMR/MMRV 7.0%; MMR/MMR+V 10.7%), followed by redness (8.6%, 4.7% and 3.6%, respectively) and swelling (4.6%, 2.9% and 3.6%, respectively) [19]. Post-dose 2, solicited local symptoms occurred in <6.5% subjects in any group. Any grade fever occurred in 13.2-32.2% children during the first 15 days post-vaccination, and there was no significant difference between the incidences of fever after the different vaccines (overlapping confidence intervals). The incidence of fever was lower post-dose 2 (***Table* I**). Post-dose 1, ≥1 unsolicited adverse event occurred in 20.6% (MMRV/MMRV), 21.7% (MMR/MMRV) and 20.0% subjects (MMR/MMR+V), compared with 10.6%, 10.0% and 12.2%, respectively post-dose 2. The most frequent unsolicited adverse events included upper respiratory tract infection, cough, nasopharyngitis and rhinitis. No episode of febrile convulsion occurred during six weeks post-vaccination. However, this was a

TABLE I FEVER DURING 0-14 DAYS FOLLOWING THE SECOND DOSE OF MMR+/-V VACCINE IN CONTROLLED CLINICAL TRIALS

Reference	*Dosing schedule*	*Vaccine administered as dose 2*	*Incidence of fever (%)*		
			N	*Any grade*	*Grade 3*
Schuster, *et al.* [14]	10-21 mo age at 1st vaccination.	MMRV	725	36.8	3.6
	2 doses MMRV 6 wks apart	MMR+V	236	33.1	4.7
Knuf, *et al.* [15]	12-24 mo at age of 1st vaccination.	MMRV	356	43.1	6.0
	2 doses MMRV 6-8 wks apart	MMR+V	116	47.5	5.7
Halperin, *et al.* [17]	MMR + V ≥6 wks before MMRV	MMRV	195	19.0	2.1
	at 15-75 mo	MMR+V	195	16.0	3.1
Gillet, *et al.* [18]	MMR ≥6 wks before MMRV at 15-24 mo	MMRV	228*	40.9	2.7
		MMR+V	230*	31.5	2.8
	MMR ≥6 wks before MMRV at 2-6 y	MMRV	228#	16.4	2.6
		MMR+V	230#	20.7	2.6
Lalwani, *et al.* [19]	MMR/MMRV or MMR/MMR+V at 9 and 15 mo	MMRV	159	13.2	1.3
		MMR+V	79	15.2	0

**Includes children aged 2-6 years; #Includes children aged 15-24 months.*

relatively small trial and may not necessarily have captured a rare side effect, which can only be seen post-marketing when more doses are administered.

DOSING SCHEDULE

MMRV vaccines have been used for over a decade worldwide and considerable post-marketing experience exists. In USA [26] and Germany [27], where the first varicella dose coincides with first MCV dose, MMR+V is preferred over MMRV due to higher rates of fever and two-fold higher febrile convulsion rates. However, there is no increased risk of febrile convulsion when MMRV vaccine is administered as 2nd dose of MCV, irrespective of the age at which the second dose is administered.

In USA, where the recommended age for the second routine MMRV dose is 4-6 years, the second dose may be administered three months after first dose. In this situation, MMRV vaccine is preferred (over MMR+V) in children ≥15 months to 12 years of age [26]. In Germany, MMRV can be administered as a second dose in 15- to 23-month-old children [27]; and in Australia [28], MMRV is exclusively provided to children at 18 months, following previous vaccination with MMR at 12 months.

In India, first dose of MCV is administered at 9-12 months; children receive their first varicella dose with 2nd dose of MCV in the second year of life. Considering the benefit-risk profile of MMRV, there are many possible scenarios for vaccine implementation in India. Complexity is added by individual practitioner-preference related to timing and number of doses of MCV. Two MMRV doses can be administered six weeks apart in children ≥12 months, but taking into account the current IAP recommendations for MMR and Varicella vaccines, and the individual preferences of private practitioners, the most feasible likely schedules are suggested in ***Table* II**. Additionally, for catch-up MMRV vaccination up to 12 years, as well as for children who miss MCV at 9-12 months, two MMRV doses can be administered with an interval of ≥6 weeks.

CO-ADMINISTRATION

The number of clinic appointments can be further reduced, and the acceptability of immunization schedules improved, by co-administering MMRV with vaccines against other diseases at the same visit. MMRV has been administered concurrently with the childhood vaccines that are scheduled at similar times; for example, diphtheria-tetanus-acellular pertussis-inactivated polio-virus vaccine-hepatitis B/Haemophilus influenzae

TABLE II FEASIBLE USAGE SCHEDULES FOR MMRV VACCINE IN INDIA

	Age			
	9 mo	*15 mo*	*18 mo*	*4-6 yr*
Option 1	MCV1	MMRV	-	MMRV
Option 2	MCV1	MMRV	V	MMR
Option 3	MCV1	MMRV	MMRV	-

MCV1: MMR, M or MR. M: monovalent measles vaccine; V: monovalent varicella vaccine; MR: bivalent measles and rubella vaccine; MMR: trivalent measles, mumps and rubella vaccine; MMRV: quadrivalent measles, mumps, rubella and varicella vaccine.

(DTPa-HBV-IPV/Hib), hepatitis B, meningococcal and pneumococcal vaccines [29-32].

Concurrent MMRV plus DTPa-HBV-IPV/Hib vaccines, were compared with single doses of either vaccine in 451 healthy children aged 12-23 months. At 42 days post-vaccination, no differences in seroconversion rates for measles, mumps, rubella and varicella, or immune responses to the DTPa-HBV-IPV/Hib antigens were seen. There were no differences in GMTs between the two groups, apart from measles, which were higher after MMRV than MMR+V. Additionally, when co-administered, there was no evidence of any exacerbation in the reactogenicity of either vaccine [29]. A large multi-center trial comparing either concurrent MMRV, Hib/HepB and DTaP, or MMRV or MMR+V followed by Hib/HepB and DTaP 42 days later, in 1915 healthy children aged 12-15 months showed similar safety profiles and antibody responses to all antigens in all groups [30].

CONCLUSION

MMR and varicella vaccines have been available in the market in India for several years and quadrivalent MMRV, which simultaneously protects against all four viruses, has recently become available. Fever rates are usually high when MMRV vaccine is administered as first dose of MCV; fever (and febrile convulsion) rates are higher than for MMR or concomitant MMR+V. However, controlled trials indicate comparable fever rates after a second MMRV dose or when MMRV dose is administered as 2nd dose of MCV.

In India, as MMRV is indicated for children ≥12 months, this vaccine will predominantly be administered as 2nd MCV. One or two MMRV doses can therefore be introduced into the Indian immunization schedule to offer broad disease protection and to provide the general advantages of combination vaccines to vaccinees, parents and physicians.

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WEB TABLE I POST-DOSE SEROCONVERSION RATES AND GEOMETRIC MEAN TITRES (GMTS) RECORDED IN MMRV TRIALS

Reference	*Age at first vaccination*	*Vaccine*	*Dose*	*Post-dose time point*	*N Immuno-genicity cohort*	*Seroconversion (%)*				*GMT (95% CI)*			
						Measles	*Mumps*	*Rubella*	*Varicella*	*Measles*	*Mumps*	*Rubella*	*Varicella*
Knuf, *et al.* [13]	10-21 mo	MMRV	2	42-56 d	141*	99.3	100	100	100	4451 (3844-5155)	2298 (2064-2558)	93 (84-104)	3389 (2768-4148)
	10-21 mo	MMRV	2	42-56 d	142#	98.6	99.3	100	100	4184 (3618-4838)	2195 (1968-2448)	106 (95 -119)	2576 (2082-3187)
Schuster, *et al.* [14]	10-21 mo	MMRV	1	42 d	681	94.5	96.1	99.7	95.5	2584(2365-2825)	158(143-174)	63(59-67)	80(73-89)
		MMRV	2	42 d		98.3	99.4	99.7	99.7	3756(3473-4062)	589(543-640)	123(116-129)	1903(1716-2111)
		MMR+V	1	42 d	219	93.4	93.6	98.1	95.6	1645(1399-1935)	124(104-149)	83(73-94)	84(70-100)
		MMR	2	42 d		97.6	99.5	100	97.5	2176(1878-2521)	449(390-516)	136(124-148)	80(66-98)
Knuf, *et al.* [15]	12-18 mo	MMRV	2	42-56 d	311	100	98.0	100	100	6104(5640-6606)	1465(1344-1598)	102(95-109)	4932(4215-5771)
Knuf, *et al.* [16]				3 yr	225§	98.5	97.4	100	99.4	3600(3135-4134)	1755(1549-1987)	52(46-59)	226(181-281)
		MMR+V	2	42-56 d	108	100	99.1	100	100	3719(3184-4345)	1668(1442-1929)	107(95-120)	155(126-190)
				3 yr	79§	97.0	93.8	100	96.8	1819(1408-2350)	1455(1128-1875)	54(44-66)	106(60-188)
Halperin, *et al.* [17]	15-75 mo	MMRV	2	Pre-dose 2	189	96.3	97.4	100	96.2	1872(1604-2185)	1381(1205-1584)	86(75-97)	93(73-118)
				42 d		100	100	100	100	2375(2112-2672)	3941(3626-4283)	159(148-172)	2533(2140-2998)
		MMR+V	2	Pre-dose 2	189	96.8	91.4	99.5	99.5	2077(1785-2416)	1101(939-1291)	78(68-90)	97(80-120)
				42 d		99.5	99.5	100	100	2788(2471-3146)	3623(3268-4016)	162(150-175)	2555(2187-2985)
Gillet, *et al.* [18]	15-24 mo	MMRV	2	Pre-dose 2	88	87.5	92.0	96.6	-	1486(1090-2024)	927(957-1136)	93(75-114)	
				42 d		98.9	100	100	97.6	2428(1971-2992)	5663(4797-6684)	123(107-141)	93(72-121)
		V	2	42 d					100				1312(1048-1644)
		MMR+V	2	Pre-dose 2	97	97.9	95.7	100	-	2147(1774-2598)	1224(1009-1484)	105(90-122)	
				42 d		99.0	100	100	100	2677(2271-3154)	4763(4113-5516)	145(128-165)	144(119-174)
		V	2	42 d					100				1415(1163-1722)
	2-6 years	MMRV	2	Pre-dose 2	107	95.3	92.5	99.1	-	1812(1434-2289)	1349(1098-1656)	90(76-108)	
				42 d		100	100	100	97.9	2833(2396-3349)	6604(5702-7648)	166(149-185)	88(65-120)
		V	2	42 d					100				1110(886-1389)
		MMR+V	2	Pre-dose 2	100	97.0	92.0	98.0	-	2144(1750-2626)	1327(1063-1656)	73(60-88)	
				42 d		100	100	100	96.6	3011(2573-3523)	5167(4486-5952)	156(140-173)	88(67-114)
		V	2	42 d					100				1145(917-1629)
Lalwani, *et al.* [19]	9-15 mo	MMRV	1	Pre-dose 1	151	1.3	1.3	0.7	7.4				

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Reference	*Age at first vaccination*	*Vaccine*	*Dose*	*Post-dose time point*	*N Immunogenicity cohort*	*Seroconversion (%)*				*GMT (95% CI)*			
						Measles	*Mumps*	*Rubella*	*Varicella*	*Measles*	*Mumps*	*Rubella*	*Varicella*
			1	43 d		93.2	86.1	98.7	94.2	2014(1662-2439)	992(820-1200)	45(38-54)	121(91-160)
		MMRV	2	43 d		100	100	100	100	4471(3975-5029)	6428(5775-7155)	148(136-162)	5319(4319-6550)
		MMR	1	Pre-dose 1	156	1.9	1.9	2.6	8.3				
			1	43 d		88.2	84.2	99.3	2.8	1180(963-1447)	747(628-888)	64(56-73)	2.2(2.0-2.4)
		MMRV	2	43 d		100	100	100	98.6	3359(3018-3738)	10109(9224-11078)	165(152-179)	198(158-248)
		MMR	1	Pre-dose 1	75	2.7	2.7	1.7	2.7				
			1	43 d		87.5	83.3	100	1.4	1200(888-1622)	775(601-1000)	62(51-75)	2.2(1.8-2.6)
		MMR+V	2	43 d		100	100	100	95.8	2495(2064-3015)	4925(4201-5775)	173(153-196)	128(92-179)

**Intramuscular injection; #Subcutaneous injection; §Persistence cohort; GMT: geometric mean titres; MMR: trivalent measles, mumps and rubella vaccine; V: monovalent varicella vaccine; MMRV: quadrivalent measles, mumps, rubella and varicella vaccine.*