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Safety and immunogenicity of a measles–mumps–rubella–varicella vaccine given as a second dose in children up to six years of age☆

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ABSTRACT

Two doses of measles–mumps–rubella vaccine (MMR) are widely recommended and consideration is being given to a similar schedule for varicella vaccine. A combined measles–mumps–rubella–varicella vaccine (MMRV) could be considered for this second dose in children previously vaccinated separately with MMR and varicella vaccines. Healthy children ($N = 390$) aged 15–75 months (median 54 months) previously immunized with MMR and varicella vaccines were randomly allocated to receive MMRV or separate injections of MMR and varicella vaccines. Before administration of study vaccines, seropositivity rates were 96.4% for measles, 94.3% for mumps, 99.5% for rubella, and 97.9% for varicella. Post-immunization, seropositivity rates were 99.5% for measles and mumps and 100% for rubella and varicella in the MMR + varicella group and 100% for all four antigens in the MMRV group; a 26.2- and 27.2-fold increase in varicella titer was observed in the MMR + varicella vaccine and MMRV groups, respectively. Except for more frequent pain in the MMRV group (33.3% vs. 23.7%, $p = 0.043$), there were no differences in the incidence of local and solicited symptoms between groups. In children primed with MMR and varicella vaccine, MMRV had non-inferior immunogenicity and similar safety profiles as a second dose of licensed MMR and varicella vaccine administered concomitantly.

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1. Introduction

For well over a decade, two-dose measles vaccine schedules have been recommended for optimal measles control [1,2]. With one-dose measles vaccine programs, outbreaks of measles continued to occur, despite high rates of vaccine uptake [3–5]. Progress toward achieving the goal of measles elimination has only been possible through implementation of the two-dose regimen [6]. Recently outbreaks of mumps in highly immunized populations have disproportionately affected older adolescents and young adults who had only received one dose of mumps vaccine since most younger children in industrialized countries received their two doses of measles vaccine as a combined measles–mumps–rubella vaccine (MMR) [7–9]. This has led to new recommendations for two-dose mumps vaccine programs including immunization of at-risk youth who had previously only received one dose of mumps vaccine [10]. In the United States, a two-dose varicella vaccine schedule was recommended after increasing reports of breakthrough infection in children immunized with a single dose [11,12], likely due to primary and secondary (waning immunity) vaccine failures [13], and consideration is being given to two-dose varicella vaccine regimens elsewhere [14,15].

Combination vaccines may provide a number of benefits including increased convenience, improved compliance, improved record-keeping, decreased pain from injections, decreased cost, and improved public acceptance [16,17]. A combined measles–mumps–rubella–varicella vaccine (MMRV) would facilitate implementation of a two-dose varicella vaccine program. During the transition from a one-dose to a two-dose schedule, there will be children eligible to receive MMRV for the second dose

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Table 1
Study vaccine composition.

Vaccine	Name	Measles Schwarz ($CCID_{50}$)[a]	Mumps RIT4385 ($CCID_{50}$)	Rubella RA27/3 ($CCID_{50}$)	Varicella OKA (pfu)[b]
MMRV	(*Priorix-Tetra*™)[c]	$\geq 10^{3.0}$	$\geq 10^{4.4}$	$\geq 10^{3.0}$	$\geq 10^{3.3}$
MMR	(*Priorix*™)[c]	$\geq 10^{3.0}$	$\geq 10^{3.7}$	$\geq 10^{3.0}$	–
Varicella	(*Varilrix*™)[c]	–	–	–	$\geq 10^{3.3}$

[a] $CCID_{50}$: median cell culture infective dose.
[b] pfu: plaque forming unit.
[c] *Priorix*, *Priorix-Tetra* and *Varilrix* are trade marks of the GlaxoSmithKline group of companies.

of measles, mumps, rubella, and varicella vaccination who had received their first dose as separate MMR and varicella vaccines. The purpose of this study was to assess the safety and immunogenicity of an MMRV vaccine in children previously immunized with one dose of MMR and varicella vaccines given as separate injections.

2. Methods

2.1. Vaccines

Three vaccines were used for the study: MMR (*Priorix*™), varicella (*Varilrix*™), and MMRV (*Priorix-Tetra*™); the former two were licensed products. All vaccines (Table 1) were manufactured by GlaxoSmithKline Biologicals (Rixensart, Belgium). A single lot of MMR and MMRV were used in the study. Two lots of varicella vaccine were used; one in Italy and one in Canada.

2.2. Study population

Healthy children between 15 months and six years of age were recruited into the study. All children needed documented evidence of having received one dose of an MMR vaccine and one dose of a varicella vaccine at least 6 weeks prior to entry into the study. Children were excluded from participation if they had already received a second dose of MMR or varicella vaccine, if there was a history of measles, mumps, rubella or varicella disease, or a known exposure to measles, mumps, rubella or varicella disease in the previous 30 days. Children were also excluded if there was a plan to administer another vaccine within 30 days before or after the study vaccine, if they had received immunosuppressive medication or immunoglobulin in the 6 months before receipt of study vaccine, or if they had a history of neurological disease or seizures, allergic disease, or personal or family history of immunodeficiency. Finally, children were excluded if they resided in a household with a newborn infant, an individual with an immunodeficiency, or a pregnant woman with a negative history of varicella infection or immunization.

2.3. Study design and procedures

The study was an unblinded, randomized, controlled, six-center study. Participants' parents or legal guardians provided written informed consent prior to any study procedure; the study was approved by the Research Ethics Board of each participating center. Participants were randomly allocated to receive either one dose each of MMR and varicella vaccines in opposite limbs or a single dose of MMRV performed using a central randomization system on Internet (SBIR) using a minimization procedure accounting for center. Randomization was in a 1:1 ratio with a block size of 4.

Vaccines were given as subcutaneous injections in the deltoid region. Participants were monitored by study staff for 30 min after the injection for immediate reactions and by their parents for injection site reactions for 4 days (days 0–3) and for general adverse events for 43 days (days 0–42) post-immunization by completing a standardized symptom diary. Temperature was measured daily for days 0–14 with a supplied digital thermometer and screened with a temperature pad for days 15–42. Solicited adverse events were either measured (fever, erythema, swelling) or categorized as mild (awareness of symptom but easily tolerated), moderate (discomfort sufficient to cause interference with usual activity) or severe (incapacitating with inability to do usual activity). Any rashes post-immunization were examined by investigators and classified as measles/rubella-like rashes, varicella-like rashes, or other rashes; an attempt to collect lesion samples for PCR for varicella virus isolation was undertaken when appropriate. Investigators were instructed to collect saliva for virus isolation should any participant have parotid swelling, and were requested to obtain a sample of cerebrospinal fluid for testing if any participant reported neurological symptoms and if it was clinically indicated. All unsolicited adverse events were collected and tabulated by MedDRA (Medical Dictionary for Regulatory Activities) primary system organ class. Blood was collected by venipuncture before and 42–56 days post-immunization. Anti-measles, anti-mumps, and anti-rubella antibodies were measured by enzyme immunoassay (*Enzygnost*™, Dade Behring, Marburg, Germany); anti-varicella antibodies were measured by immunofluorescent antibody assay (*Virgo*™, Hemagen Diagnostics, Columbia, MD with modifications). All testing was done in a blinded fashion on sera in the laboratories of GlaxoSmithKline Biologicals in Rixensart, Belgium.

2.4. Data analysis and statistical considerations

All subjects who received a dose of vaccine were included in the analysis of safety (total vaccinated cohort). Adverse events were tabulated and the maximum severity reported was used for each time period. Grade 3 reactions were defined as measured reactions >20 mm in diameter, temperature >39.5 °C (rectal) and all other adverse events preventing normal, everyday activities were assessed as severe. The proportion of participants having an adverse event for each vaccine group and for grade 3 severity was calculated with exact 95% confidence intervals and, for solicited adverse events, compared by Fisher's exact test. A value of $p < 0.05$ was used to explore possible differences between groups and statistical significance findings should be interpreted with caution. No adjustments were made for multiple comparisons.

All subjects who had serum specimens collected according to the protocol-specified criteria were included in the analysis (according-to-protocol analysis of immunogenicity cohort). Geometric mean antibody titers (GMT) were calculated with 95% confidence intervals for antibodies against each vaccine component pre- and 42 days post-immunization. Subjects without a pre-immunization result were not included in the analysis. With respect to GMTs, log-transformed titers were assumed normally distributed with an unknown variance. The 95% confidence intervals for GMTs were obtained by exponential transformation of the 95% confidence interval for the mean of log-transformed titer. Antibody concentrations below the assay cut-off were given an arbitrary value of half the cut-off. Non-inferiority of the two groups was declared if the lower limit of the 95% confidence interval for the GMT ratio of

Table 2
Characteristics of the study population.

Characteristics		MMRV	MMR + varicella	Total
Total vaccinated subjects	*N*	195	195	390
Age	Mean ± SD[a], months	47.4 (±19.18)	46.6 (±19.08)	47.0 (±19.11)
Gender	Female (%)	49.2	53.8	51.5
	Male (%)	50.8	46.2	48.5
Race	Caucasian/European heritage	91.8	92.8	92.3

[a] SD: standard deviation.

the MMRV group over the MMR + varicella group was >0.67. The 95% confidence interval for the GMT ratio was computed using an ANCOVA model on the log-transformed titers. The ANCOVA model includes the vaccine group as the fixed effect and the pre-immunization log-transformed titers as the regressor. A sample size of 400 was selected to account for an estimated 10% of participants who may not be evaluable for the analysis and to provide 90% power for the non-inferiority of the four immunogenicity outcomes.

A post hoc age-related analysis was performed to explore the safety and immunogenicity of the MMRV and MMR + varicella vaccines in toddlers (24 months of age or younger) and children over 2 years of age.

3. Results

3.1. Demographics and participant disposition

A total of 390 participants were enrolled in the study equally allocated to receive MMR + varicella or MMRV. All but two (99.5%) participants, both in the MMR + varicella group, completed the study; parental withdrawal of consent accounted for both participants who did not complete the study. All participants were included in the total vaccinated population (for safety analysis). Twelve participants were excluded from the per-protocol immunogenicity analysis (six from each group); one lacking pre-vaccination serum (MMRV group) and nine who lacked a post-vaccination serum sample (six in the MMR + varicella group and three in the MMRV group including seven for whom serum was missing and the two who withdrew from the study). The final two exclusions from the immunogenicity analysis (both in the MMRV group) consisted of a participant who had received two previous MMR doses and a participant who had not received a previous MMR dose.

Participant demographic characteristics did not differ by study group (Table 2).

3.2. Adverse events

All vaccines were well tolerated by participants and in general had similar adverse event profiles. During the 43 days post-immunization, an adverse event, either solicited or unsolicited, was reported by 70.3% (95% confidence interval 63.3–76.6) of MMRV recipients and 65.6% (58.5–72.3) of MMR + varicella recipients. Both injection site events (52.3% [45.1–59.5] in the MMRV group and 41.5% [34.5–48.8] in the MMR + varicella group) and general adverse events (47.2% [40.0–54.4] in the MMRV group and 48.2% [41.0–55.5] in the MMR + varicella group) were frequently reported. There were no differences in the incidence of solicited general symptoms between groups but the overall incidence of pain reported at any injection site during the first 3 days post-immunization was higher in the MMRV group (MMRV: 33.3% [26.8–40.4], MMR + varicella: 23.7% [17.9–30.3], $p = 0.043$) (Table 3). Among the recipients of separate injections of MMR and varicella vaccines, pain, redness and swelling were more common at the varicella injection site than the MMR site. During the 15 days post-vaccination, no difference was observed between groups in the incidence of any fever (MMRV: 19.0% [13.7–25.2] and MMR + varicella: 16.0% [11.1–21.9]), and in the incidence of grade 3 fever (MMRV: 2.1% [0.6–5.2] and MMR + varicella: 3.1% [1.1–6.6]).

During the 43 days post-vaccination, a rash was reported by 15.4% (10.6–21.2) of MMRV recipients and 11.9% (7.7–17.3) of MMR + varicella recipients. A measles/rubella-like rash was reported by 2.1% (0.6–5.2) of both groups; a varicella-like rash was reported by 1.5% (0.3–4.4) of MMRV recipients and 0.0% (0.0–1.9) of MMR + varicella recipients. Varicella virus could not be isolated from the lesions. There were no instances of parotid swelling, meningismus, or febrile seizures. The most common unsolicited adverse events were irritability (5.6% and 5.1% in MMRV and MMR + varicella recipients, respectively), cough (5.1% and 3.6%), vomiting (4.6% and 4.1%), diarrhea (5.1% and 5.1%) and upper respiratory infection (4.6% and 3.1%). Only one serious adverse event was reported during the study (hospitalization for pharyngitis 7 days after MMR + varicella) which was deemed by the investigator to be unrelated to immunization. In the post hoc age-related analysis of safety, both general adverse events and adverse events associated with the injection sites were reported more commonly in toddlers than in older children, regardless of whether they received MMRV or MMR + varicella vaccines. In recipients of MMRV, injection site redness was reported by 74.4% (58.8–86.5)

Table 3
Incidence of solicited local and general symptoms after vaccination. Population analyzed was the total vaccinated cohort (all subjects who received a dose of vaccine).

Local symptoms (days 0–3, % with 95% CI)		MMRV	MMR + varicella		
			MMR + varicella	MMR injection site	Varicella injection site
Pain	Any	33.3 (26.8, 40.4)	23.7 (17.9, 30.3)	13.4 (8.9, 19)	21.1 (15.6, 27.6)
	Grade 3[a]	1.0 (0.1, 3.7)	0.0 (0.0, 1.9)	0.0 (0.0, 1.9)	0.0 (0.0, 1.9)
Redness	Any	36.9 (30.1, 44.1)	31.4 (25.0, 38.5)	12.9 (8.5, 18.4)	28.4 (22.1, 35.2)
	>20 mm	14.4 (9.8, 20.1)	8.2 (4.8, 13.0)	0.5 (0.0, 2.8)	7.7 (4.4, 12.4)
Swelling	Any	22.6 (16.9, 29.1)	21.1 (15.6, 27.6)	6.2 (3.2, 10.6)	20.6 (15.2, 27.0)
	>20 mm	5.6 (2.8, 9.9)	4.1 (1.8, 8.0)	0.5 (0.0, 2.8)	4.1 (1.8, 8.0)
Fever (days 0–14, % with 95% CI)					
All	(≥38 °C)	19.0 (13.7, 25.2)	16.0 (11.1, 21.9)		
Grade 3	(>39.5 °C)	2.1 (0.6, 5.2)	3.1 (1.1, 6.6)		

[a] Cries when limb is moved or spontaneously painful.

Table 4
Geometric mean antibody titers before and after immunization with one dose of MMRV or MMR plus varicella vaccines. Population analyzed was the according-to-protocol cohort for immunogenicity.

Antigen		MMRV		MMR + varicella			Ratio GMTs post-/pre-vaccination		Adjusted GMT ratio (MMRV/MMR + varicella) (95% CI)
		N[a]	GMTs (95% CI)	Adjusted GMT[b]	N	GMTs (95% CI)	Adjusted GMT	MMRV	MMR + varicella	
Measles	Pre	189	1872.2 (1603.9, 2185.4)	2448.2	189	2076.7 (1785.2, 2415.8)	2705.1	1.27 (1.14; 1.41)	1.34 (1.22; 1.48)	0.91 (0.81, 1.01)
	Post	189	2375.3 (2111.8, 2671.7)		189	2788.1 (2470.7, 3146.2)				
Mumps	Pre	189	1381.4 (1205.1, 1583.5)	3798.1	186	1100.9 (938.9, 1290.8)	3761.4	2.85 (2.53; 3.21)	3.29 (2.87; 3.77)	1.01 (0.90, 1.13)
	Post	189	3940.9 (3626.1, 4283.0)		186	3622.9 (3268.1, 4016.2)				
Rubella	Pre	189	86.0 (76.4, 96.9)	156.8	189	78.3 (68.4, 89.6)	164.3	1.85 (1.68; 2.05)	2.07 (1.85; 2.30)	0.95 (0.87, 1.04)
	Post	189	159.4 (147.7, 172.0)		189	161.7 (149.7, 174.6)				
Varicella	Pre	186	93.2 (73.4, 118.5)	2551.2	188	97.4 (78.9, 120.4)	2536.7	27.16 (21.70; 33.99)	26.22 (21.63; 31.79)	1.01 (0.82, 1.23)
	Post	186	2532.7 (2139.6, 2998.0)		188	2555.1 (2187.0, 2985.0)				

[a] *N*: number of subjects with pre- and post-vaccination results available.
[b] Adjusted GMT: geometric mean antibody titer at post-vaccination adjusted for baseline titer (ANCOVA model: adjustment for baseline titer-pooled variance).

of toddlers and 26.3% (19.5–31.1) of older children ($p < 0.001$). In recipients of MMR + varicella vaccines, redness was reported by 54.3% (39.0–61.1) of toddlers and 24.3% (17.7–32.1) of older children ($p < 0.001$). Swelling was reported by 34.9% (21.0–50.9) of toddlers and 19.1% (13.2–26.2) of older children recipients of MMRV ($p = 0.038$) and by 39.1% (25.1–54.6) of toddlers and 15.5% (10.1–22.4) of older children recipients of MMR + varicella vaccines ($p = 0.002$). There were no apparent age-related differences in injection site pain or general adverse events in either vaccine group (data not shown).

3.3. Antibody response

Pre-immunization antibody levels were similar between the groups for all viruses; a vigorous antibody response was elicited by both MMRV and MMR + varicella vaccines (Table 4). There were no statistically significant differences between the groups for post-immunization geometric mean antibody levels against measles, mumps, rubella, or varicella. The criteria for concluding non-inferiority of MMRV vs. MMR + varicella vaccines were met since the lower limits of the 95% confidence intervals for all geometric mean antibody titers were above the pre-defined limits of 0.67 (measles: 0.91 [0.81–1.01]; mumps: 1.01 [0.90–1.13]; rubella: 0.95 [0.87–1.04]; varicella: 1.01 [0.82–1.23]) (Table 4).

Before immunization, 96.3% of the MMRV group and 96.8% of the MMR + varicella vaccine group were seropositive (≥150 mIU/mL) for measles antibody, 97.4% and 91.4% respectively were seropositive (≥231 U/mL) for mumps antibody, 100% and 99.5% respectively were seropositive (≥4 IU/mL) for rubella antibody, and 96.2% and 99.5% respectively were seropositive (≥4 reciprocal dilution) for varicella antibody. Post-immunization, 100% of MMRV recipients and 99.5% of MMR + varicella vaccines recipients were seropositive against measles. All seven MMRV recipients who were initially seronegative became seropositive and five (83.3%) of six initially seronegative MMR + varicella vaccines recipients became seropositive for measles antibody. After immunization, all MMRV recipients including five participants initially seronegative were seropositive for mumps antibody. In the MMR + varicella vaccines group, 99.5% of participants including all 16 initially seronegative participants were seropositive for mumps antibody. For rubella antibody, only one participant (in the MMR + varicella vaccines group) was seronegative before immunization; all participants were seropositive after immunization. All participants were seropositive for varicella antibody post-immunization including seven participants in the MMRV group and one participant in the MMR + varicella vaccines group who were initially seronegative.

In the post hoc age-related analysis, there were no differences in geometric mean antibody titers or in seropositivity rates between toddlers and older children pre- or post-immunization except for higher rubella antibody titers in toddlers pre-immunization (data not shown).

4. Discussion

The results of this study show that MMRV was well tolerated and immunogenic when given as a second dose to toddlers and children previously immunized with separate injections of MMR and varicella vaccines. This study was designed to evaluate the scenario where MMRV is introduced into a country where MMR and varicella vaccines are already being used, particularly where a second dose of varicella vaccine is recommended. In this situation, a transition period will exist where children who require a second dose of MMR and varicella vaccines (given as MMRV) have received their first immunization with separate injections of MMR and varicella vaccines. This study was undertaken to demonstrate the non-inferiority of a second dose given as MMRV compared

to separate injections of MMR and varicella vaccines. The non-inferiority criteria (the requirement for the lower limits of the 95% confidence interval for the GMT ratios between MMRV and MMR + varicella vaccines to be above 0.67) were fulfilled for all vaccine antigens. Age-related immunogenicity was explored as well in a post hoc analysis that also assessed the similarity between the immune responses to MMRV and to the separate MMR and varicella vaccines. The safety profiles of the combination and separate vaccines were also similar although injection site adverse events were more commonly reported after MMRV than MMR, perhaps suggesting the increased injection site reactions were related to the varicella component. No vaccine-related serious adverse event (including febrile seizures) was reported in either group.

Two doses of MMR vaccine are now standard in most developed countries because outbreaks of measles were still frequently observed despite high one-dose vaccine coverage [1,2,5]. Indeed, in order to meet the objective of worldwide measles elimination, the World Health Organization now recommends that all countries implement a two-dose measles vaccine schedule [2]. Recent outbreaks of mumps in the United States [7] and Canada [9] have been concentrated in adolescents and young adults who had only received one dose of MMR before the two-dose measles recommendation was implemented. These outbreaks are thought to be due to both primary vaccine failure after a single dose as well as waning immunity (secondary vaccine failure). Immunization programs targeted to provide a second dose of MMR to university-aged youth have been implemented in an attempt to control the resurgence of mumps [10].

Varicella vaccination is part of the routine immunization schedule in the United States, Canada, and Australia; to date, only a few countries or regions in Europe (Germany, Greece, and several regions of Italy) have implemented a universal varicella immunization program [18,19]. In the United States, the first country to implement a universal program, the incidences of varicella, varicella hospitalizations, and complications of varicella including deaths dropped dramatically as coverage with varicella vaccine increased [20,21]. With time, however, there were increasing reports of cases of varicella in daycare facilities and schools despite high rates of vaccine coverage [22–27]. Cases occurred both among those who had not been immunized as well as those who had received a single dose of varicella vaccine. The risk of breakthrough infections increased with time elapsed since immunization, as did their severity, although these diseases tended to be less severe than diseases in unimmunized children [13,28]. The purpose of the second dose is therefore both to immunize those who did not respond to the first dose and to bolster a waning immunity in previously immunized responders.

Other jurisdictions currently using a one-dose varicella vaccine schedule are now considering following the lead of the United States in using a two-dose schedule. In these jurisdictions, a combination MMRV vaccine that is well tolerated and immunogenic in toddlers and young children already immunized with a single dose of MMR and varicella vaccine would facilitate this program change. Combination vaccines provide an effective method for improving compliance and increasing vaccine coverage. They are more convenient, improve record keeping, can be more cost-effective, and in most instances are preferred by parents, children, and health care providers to multiple injections [17].

The MMRV vaccine studied in this clinical trial has been shown to be well tolerated and immunogenic when given as the second dose in children previously immunized with separate injections of MMR and varicella vaccines. This profile has already been observed when this MMRV vaccine was given as a two-dose series [29–32]. With its recent licensure in many countries within the European Union and internationally, MMRV will facilitate achieving the goals of measles elimination and the control of mumps, rubella and varicella.

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