

Safety, Reactogenicity and Immunogenicity of the Live Attenuated Combined Measles, Mumps and Rubella Vaccine Containing the RIT 4385 Mumps Strain in Healthy Singaporean Children

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Abstract

Introduction: Measles, mumps and rubella (MMR) are viral infections causing significant mortality and morbidity for which effective and safe vaccines are available. The safety, reactogenicity and immunogenicity of a combined MMR vaccine when administered to healthy Singaporean children were evaluated in this study. **Materials and Methods:** A total of 150 children aged 12 to 18 months were vaccinated in this open, single-group, single-centre study [209762/147]. Solicited local and general symptoms reported within 4 days of vaccination and fever, parotid/salivary gland swelling and signs of meningism in the 43 days following vaccination were recorded using diary cards. Serious adverse events occurring during the study period were monitored. Immunogenicity was assessed at 42 days post-vaccination. **Results:** Redness (8.7%) and pain (7.2%) at injection site were the most commonly reported solicited local symptoms during the 4-day follow-up period after vaccination. Percentage of subjects reporting drowsiness, irritability and loss of appetite during the 4-day follow-up after vaccination was 7.2%, 8% and 7.2%, respectively. None of the solicited symptoms reported during the 4-day follow-up period was of grade “3” intensity. Fever (42.8%) was the most commonly reported solicited general symptom, with 5.1% of the children reporting fever >39.0°C (axillary). No serious adverse events considered to be related to vaccination were reported. Seroconversion rates were 100% for measles and rubella antibodies and 98.1% for mumps antibodies. **Conclusions:** GlaxoSmithKline Biologicals’ MMR vaccine was shown to be well tolerated and highly immunogenic when used in Singaporean children 12 to 18 months of age.

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Introduction

Measles, mumps and rubella (MMR) are contagious viral diseases associated with high mortality and morbidity, often linked with severe complications. Globally, measles remains the main cause of vaccine-preventable morbidity and mortality in children. This is true even in the Western Pacific region, despite the fact that immunisation has reduced deaths by 95% compared with the pre-vaccine era. In 2003, there were more than 100,000 measles cases reported in this region.¹ The high incidence of mortality and complications associated with measles prompted the World Health Organization (WHO) to target measles for eradication through vaccination and to recommend offering all children 2 doses of measles or measles-containing

vaccines. This “second opportunity” measles immunisation strategy,² now adopted by most industrialised and many developing countries, is aimed at improving vaccination coverage in childhood, thereby achieving high herd immunity against measles. It also plays an important role in increasing the proportion of the population with lifelong protection against measles, as boosting through natural infection gradually disappears. Vaccination coverage of at least 95% for the first dose and at least 80% for the second dose has been listed by a panel of experts as 1 of 5 indicators of progress towards regional elimination of measles.³

Currently, the commercially available combined MMR vaccines incorporate one of several strains of mumps virus, along with the established Schwarz or Enders Edmonston

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measles vaccine strain and RA27/3 rubella vaccine strain. The several live, attenuated mumps virus vaccine strains that have been used on a wide scale include the Jeryl Lynn and Jeryl Lynn-derived RIT 4385 strain, both of which have very good protective efficacy and safety profiles,⁴ though RIT 4385-containing vaccine has been shown to be superior to the Jeryl Lynn-containing vaccine in terms of local tolerability.^{4,7} Reports that the Leningrad 3-derived L-Zagreb mumps strain and the Urabe strain are associated with an increased risk of aseptic meningitis have resulted in their withdrawal from some countries (e.g., Canada, Japan and UK).^{4,8} The low protective efficacy demonstrated by the Rubini strain has supported the WHO recommendation not to incorporate this mumps strain in national immunisation programme vaccines.⁴

The success of MMR vaccines has resulted in the current public perception of these diseases as mild illnesses of childhood. Such misperception is quickly dispelled by the grim statistic that measles, for example, is still the cause of over 600,000 child deaths globally every year.³ At the same time, concerns over the efficacy and safety of existing vaccines may erode coverage with MMR or measles-rubella vaccination. The highly infectious nature of these viruses requires that MMR vaccines must be effective and that vaccination coverage must be maintained at high levels (at least 90%) in order to interrupt transmission in populations.⁹ In countries where national immunisation programmes are capable of achieving and sustaining high coverage, the WHO recommends implementation of a routine two-dose schedule for MMR vaccination.²

In Singapore, the childhood immunisation programme offers vaccination against most vaccine-preventable childhood diseases, including MMR. Trivalent MMR vaccination in 12-month-old children was introduced in the national immunisation programme in January 1990. This was followed by a “catch-up” measles vaccination programme in 12- to 18-year-old adolescents in 1997, prompted by a significant increase in the number of reported cases of measles among youths in Singapore. Eventually, a second dose of MMR vaccine was included in the childhood immunisation programme in 1998.¹⁰ Since January 1990, mumps virus strains used in MMR vaccines in Singapore have included the Urabe strain, the Jeryl Lynn strain and the Rubini strain. The Urabe strain was withdrawn from Singapore in 1992 after reports of post-vaccination neurological complications in other countries,¹¹⁻¹³ and this strain was replaced by the Rubini strain during 1993 to 1995. Following the unexpected resurgence of mumps in Singapore in 1998, and with epidemiological data implicating the poor protection offered by the Rubini strain in Singapore,^{10,14,15} as well as countries like Spain,¹⁶ Portugal,¹⁷ and Switzerland,^{18,19} vaccines containing this

strain were withdrawn in Singapore.

GlaxoSmithKline Biologicals' MMR vaccine, *Priorix*TM, containing the RIT 4385 strain of mumps virus, which is derived from the Jeryl Lynn strain, combined with the Schwarz measles strain and the RA 27/3 rubella strain, was registered in Singapore in 1999. The safety and immunogenicity of *Priorix*TM vaccine had already been demonstrated in 22 clinical trials with more than 7500 children across the world.²⁰ The objective of the present phase IV study was to demonstrate the safety, reactogenicity and immunogenicity of this MMR vaccine in Singaporean children.

Materials and Methods

All parents and guardians coming to the polyclinic to seek MMR vaccination for their children were approached to participate in the study. A total of 150 healthy children aged 12 to 18 months was enrolled in this study [209762/147] conducted between 23 November 2000 and 17 April 2001 at Choa Chu Kang Polyclinic, 1 of 9 district clinics operated by the National Healthcare Group, which provides government-subsidised, outpatient curative, preventive and health education services covering the north-western half of Singapore.

The study was conducted according to the provisions of the Declaration of Helsinki (Somerset West, Republic of South Africa, October 1996) and Good Clinical Practice in operation at the time and was approved by the Ethics Committee of the healthcare group. Written informed consent was obtained from the parents or guardians of the children.

Children were excluded from enrollment in this study if they had a past history of measles, mumps or rubella; allergies or other reactions to neomycin or egg proteins; convulsions, epilepsy or other central nervous system diseases; or had an acute febrile illness or obvious upper respiratory tract symptoms at the planned time of vaccination. Other exclusion criteria included: chronic drug therapy; confirmed or suspected immunosuppressive condition (including human immunodeficiency virus) and administration of blood products or immunoglobulins 3 months before enrollment.

All subjects enrolled into the study received a single dose of *Priorix*TM containing live attenuated Schwarz strain (measles), RIT 4385 strain (mumps) and RA 27/3 strain (rubella) subcutaneously in the left upper arm. The titres for each virus strain were $\geq 10^{3.0}$ TCID₅₀ (tissue culture infective dose₅₀) for Schwarz measles, $\geq 10^{3.7}$ TCID₅₀ for RIT 4385 mumps and $\geq 10^{3.0}$ TCID₅₀ for RA 27/3 rubella. The measles and mumps virus strains were produced on chicken embryo fibroblasts. The rubella virus strain was produced on human diploid MRC-5 cells. The study vaccine complied with

WHO and European Pharmacopoeia requirements for viral titres per dose for each of the 3 vaccine strains. Vaccines were supplied in monodose vials containing a freeze-dried pellet to be reconstituted with an individual ampoule of water for injection. All vaccines were stored between 2° to 8°C and were reconstituted with water prior to vaccination.

Parents/guardians of all subjects were issued with a diary card on which they were to record adverse events (occurrence, start and end days of symptoms, daily measurement of the maximum diameter of any redness, swelling at the injection site and intensity of symptoms) and any medication given to the subject. Safety and reactogenicity were assessed in all vaccinees for 43 days (Day 0 to 42), with daily completion of diary cards by the parents/guardians. Details of solicited local symptoms (pain, swelling and redness) at the injection site and solicited general symptoms (drowsiness, irritability/fussiness and loss of appetite) were recorded on the diary card for the 4 days (Day 0 to 3) post-vaccination. Specific general symptoms (fever, rash, parotid/salivary gland swelling and signs of suspected meningitis) were obtained daily up to 43 days post-vaccination. Symptoms were classified according to their intensity (grade “1” to grade “3”). For pain, redness/swelling and fever, grade “3” was defined as spontaneously painful, redness/swelling of diameter >20 mm or axillary temperature >39.0°C, respectively. Swelling of parotid/salivary gland accompanied by additional symptoms was classified as a grade “3” symptom. For all other symptoms, grade “3” was defined as “preventing normal daily activities”. Parents/guardians were instructed to take their child to the investigator if salivary gland swelling or signs of suspected meningitis or central nervous system disorders such as the occurrence of febrile convulsions, vomiting, neck stiffness or photophobia were noted during the 43 days post-vaccination. The child was then to undergo neurological examination according to the current local medical practice. The occurrence of any other adverse events (both local and general) occurring during the 43-day follow-up period were recorded as unsolicited symptoms. The investigator recorded the outcome of all adverse events and assessed the causality of general and unsolicited symptoms to the vaccination. Serious adverse events that were reported during the entire study period were monitored.

Laboratory Assays

Pre- and post- (42 days) vaccination blood samples (3 mL) were taken from all vaccinees. All laboratory analyses were done at GlaxoSmithKline Biologicals' central laboratory, Rixensart, Belgium. Antibody titres were determined using commercial assays and assays were carried out according to manufacturer's instructions. Anti-measles immunoglobulin G (IgG), anti-mumps IgG and anti-rubella IgG were measured using *Enzygnost*TM (Dade Behring

Marburg GmbH, Germany) immunoassays. The assay cut-offs were 150 mIU/mL for measles, 231 U/mL for mumps and 4 IU/mL for rubella.

Statistical Analyses

Statistical analyses were performed on study subjects fulfilling the protocol-defined criteria, referred to as the according-to-protocol (ATP) cohort. The percentages of subjects reporting solicited local and general symptoms and at least one unsolicited symptom were tabulated with 95% confidence interval (CI) and presented together with intensity and relationship to vaccination. Seroconversion was defined as the appearance of antibody titres \geq to the assay cut-off, in a subject seronegative at pre-vaccination. Seroconversion rates (i.e., percentage of subjects who seroconverted) and geometric mean titres (GMTs) were calculated along with the 95% CI. GMT calculations were performed by taking the log-transformation of individual titres and calculating the anti-log of the mean of these transformed values. Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.

Results

All 150 children enrolled in this study fulfilled the inclusion/exclusion criteria. The mean age of the enrolled subjects was 15.2 months, with a standard deviation of 0.55 months. Eleven subjects were excluded from the reactogenicity analysis, of which 10 subjects had been lost to follow-up and whose data for solicited and unsolicited symptoms were thus not available, and 1 subject had received Japanese B encephalitis vaccine, which violated the study protocol. Of the 139 subjects included in the analysis of reactogenicity, a further 6 were excluded from immunogenicity analysis. Three subjects had received medication forbidden in the protocol, 2 subjects' essential serological data were missing and 1 subject had not adhered to the protocol-defined interval for the blood sampling schedule.

Data on solicited symptoms were available for a total of 138 subjects. During the 4-day follow-up period after vaccination, redness (8.7%) followed by pain (7.2%) at the injection site were the most commonly reported local symptoms. None of the solicited local symptoms reported was of grade “3” intensity. The percentage of subjects reporting drowsiness, irritability and loss of appetite was 7.2%, 8% and 7.2%, respectively. None of these symptoms prevented normal activity (Table 1).

During the 43-day follow-up period after vaccination, fever (axillary temperature \geq 37.5°C) was reported by 42.8% of subjects (59 cases); 35.5% of the cases of fever (49 of the 138 cases) occurred within the 2-week period post-vaccination. About 5% of children reported fever >39.0°C

Table 1. Incidence of Solicited Local and General Symptoms Reported Post-vaccination

Solicited local symptoms reported during the 4-day follow-up period after vaccination*

Symptom	Intensity	(N = 138)		
		n	%	95% CI
Pain	Any	10	7.2	3.5-12.9
Redness	Any	12	8.7	4.6-14.7
Swelling	Any	5	3.6	1.2-8.3

Solicited general symptoms reported during the 4-day follow-up period after vaccination*

Drowsiness	Any	10	7.2	3.5-12.9
	Related	7	5.1	2.1-10.2
Irritability	Any	11	8.0	4.0-13.8
	Related	8	5.8	2.5-11.1
Loss of appetite	Any	10	7.2	3.5-12.9
	Related	9	6.5	3.0-12.0

Solicited general symptoms reported during the 43-day follow-up period after vaccination

Febrile	Any	1	0.7	0.0-4.0
convulsion	Grade 3	1	0.7	0.0-4.0
Fever	Any ($\geq 37.5^{\circ}\text{C}$)	59	42.8	34.4-51.5
	$>39^{\circ}\text{C}$	7	5.1	2.1-10.2

* None of the symptoms reported were of grade "3" intensity.

95% CI: exact 95% confidence intervals, lower and upper limits;

Grade "3": symptom preventing normal daily activities;

n (%): number (percentage) of subjects reporting a specified symptom;

N: number of subjects with diary card completed

(axillary temperature) (Table 1). No cases of parotid/salivary gland swelling were reported. One child had febrile convulsions; details of this case are given below.

Unsolicited symptoms were reported by about 37% of the subjects (51 of 139) during the 43-day follow-up period after vaccination. Most of the symptoms reported were related to the respiratory system (23% coughing and 19.4% rhinitis). Less than 1% of subjects reported rash in the 43 days post-vaccination.

One serious adverse event was reported during the study, with the subject diagnosed as having a febrile convulsion and upper respiratory tract infection. The subject had a febrile convulsion 26 days after vaccination and was hospitalised. Neurological examination was normal, no lumbar puncture was performed and the subject recovered without sequelae. This event was not considered to be causally related to vaccination.

Of the 133 subjects in the ATP immunogenicity cohort, data on pre-vaccination serological status were available for 116 subjects, of which 104 subjects (89.7%) were

Table 2. Seroconversion rates and GMTs for anti-measles, anti-mumps and anti-rubella antibodies for initially seronegative subjects

Antibody	N	S%	GMT (95% CI)
Anti-measles	104	100	3018.5 mIU/mL (2703.6, 3370.5)
Anti-mumps	108	98.1	1132.7 U/mL (978.2, 1311.6)
Anti-rubella	115	100	78.1 IU/mL (69.2, 88.1)

95% CI: 95% confidence intervals, lower and upper limits;

GMT: geometric mean titres;

N: number of subjects with immunogenicity data available for post-vaccination blood samples taken at Day 42;

S%: percentage of subjects with titres \geq assay cut off (≥ 150 mIU/mL for measles, ≥ 231 U/mL for mumps and ≥ 4 IU/mL for rubella)Seroconversion (S) was defined as appearance of antibody titres \geq to the assay cut-off, in a subject seronegative at pre-vaccination.

initially seronegative for anti-measles antibodies, 112 (96.6%) for anti-mumps antibodies and 115 (99.1%) for anti-rubella antibodies.

All initially seronegative subjects seroconverted with respect to anti-measles and anti-rubella antibodies with GMT of 3018.5 mIU/mL and 78.1 IU/mL, respectively and all but two subjects seroconverted (98.1%) with respect to anti-mumps antibodies with GMT of 1132.7 U/mL (Table 2).

Overall, irrespective of pre-vaccination serological status, all vaccinees were seropositive after vaccination for anti-measles and anti-rubella antibodies and 98.2% of vaccinees were seropositive after vaccination for anti-mumps antibody.

Discussion and Conclusion

The safety, reactogenicity and immunogenicity of the MMR vaccine *Priorix*TM (GlaxoSmithKline Biologicals) containing the established Schwarz measles and RA27/3 rubella vaccine strains and a more recent mumps strain RIT 4385 were assessed in the local population of Singapore. In this trial, this MMR vaccine was shown to have a good reactogenicity profile. Although there was no comparative vaccine included for comparison in this study, the incidence of local and general adverse events reported in this study was similar to that observed previously with GSK-MMR vaccine. Rash was reported by < 1% of subjects in our study which was lower than the 2.7% to 7.8% previously reported in literature. Febrile convulsions were reported by 1 subject. No cases of parotid swelling were reported were reported in this study. These data are similar to other studies with MMR vaccines wherein suspected meningitis was reported by 0.1% of subjects and parotid swelling by 0% to 1.8% of subjects.²⁰

The immunogenicity observed in this population of Singaporean children, in terms of seroconversion rates to measles (100%), mumps (98.1%) and rubella (100%), was similar to other trials where *Priorix*TM was used as a first

dose in the second year of life, where seroconversion rates ranged from 96.1% to 100% for anti-measles, 91.7% to 98.6% for anti-mumps and 98.1% to 100% for anti-rubella.^{5,6,20-23} Furthermore, co-administration of a varicella vaccine with *Priorix*TM induced seroconversion rates similar to that obtained with *Priorix*TM alone.²³ These data confirm the high immunogenicity of *Priorix*TM as it has already been established that seroconversion confers immunity to subsequent exposure to the MMR virus.²⁴⁻³² Data from a recent study, conducted to investigate the efficacy of the various vaccine strains in Singapore, further provide evidence of high efficacy with the Jeryl Lynn strain (80.7%) when compared to the Urabe (54.4%) and Rubini (53.3%) vaccine strains.³³

In conclusion, GlaxoSmithKline Biologicals' MMR vaccine *Priorix*TM was shown to be well tolerated and highly immunogenic when used in Singaporean children 12 to 18 months of age.

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