A RANDOMIZED COMPARATIVE TRIAL IN ORDER TO ASSESS THE REACTOGENICITY AND IMMUNOGENICITY OF A NEW MEASLES MUMPS RUBELLA (MMR) VACCINE WHEN GIVEN AS A FIRST DOSE AT 12-24 MONTHS OF AGE

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Abstract. An open, randomized multi-center trial, involving 700 infants, was conducted in order to compare a new measles mumps rubella (MMR) vaccine, SB MMR (containing a Jeryl Lynn derived mumps strain RIT 4385) with a widely used vaccine, Merck MMR, when given to children between 12-24 months. Infants were divided between 2 groups; group 1 received SB MMR while group 2 received Merck MMR. Solicited local and general symptoms were recorded using diary cards and antibody levels were measured using ELISA assays. There was a significantly lower incidence of redness ($p < 0.001$) and swelling ($p = 0.03$) observed in group 1 compared with group 2. The incidence of all other solicited local and general symptoms were comparable between groups. In initially seronegative subjects equivalent seroconversion rates and post-vaccination GMTs were observed between groups. In conclusion, these results demonstrate that SB MMR is safe and well tolerated when given to children at this age range, and has an equivalent immunogenic profile compared to the widely used Merck MMR vaccine.

INTRODUCTION

Measles, mumps and rubella are viral diseases associated with debilitating consequences, which increase in severity with age. In the Philippines measles is the 8th cause of infant mortality. A high incidence of measles associated infant mortality has also been seen in other parts of the developing world, and consequently, measles vaccination was introduced into the Expanded Program of Immunization in 1978 (WHO, 1994). In addition, the Centers for Disease Control and Prevention (CDC) has announced the Childhood Immunization Initiative, calling for the elimination of indigenous transmission of six diseases, including measles and rubella from the United States (CDC, 1994).

In the 1980s both Europe and the United States, introduced of a two-dose strategy of combined measles mumps rubella (MMR) vaccination, which subsequently has been shown to be highly successful in reducing the incidence of these diseases (Hilleman, 1996; Peltola *et al*, 1994). This, in part, can be attributed to the use of combined MMR vaccines which allows a reduction in the number of injections and clinic visits required for children (Goldenthal *et al*, 1995), hence improving the compliance of families. This in turn allows a high vaccine coverage to be reached which is needed to modify the epidemiology of the diseases (Anderson and May, 1990). In addition, the second dose at either 4-6 or 11-12 years of age has also ensured high coverage by reaching individuals who may have not received a first dose or be primary vaccine failures (AAP, 1998).

However, one of the factors which has affected the uptake of vaccination has been concerns over side-effects (Roberts *et al*, 1995). Consequently the aim of vaccine development is to improve not only the protective capacity but also the safety profile of vaccines. Obtaining a balance between these two factors has not always proven easy. For example, while the Urabe Am 9 strain has been shown to have high immunogenicity, it has also been associated with an increased risk of aseptic meningitis (reviewed by Balraj and Miller, 1995). Although

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the benefits of vaccination with Urabe strain derived vaccines far outweigh the relatively low risk of benign cases of aseptic meningitis, vaccines containing this strain have been withdrawn from markets in certain countries (Miller *et al*, 1993; Schmitt *et al*, 1993).

In the interests of improving the tolerability of MMR vaccines, we have evaluated a new MMR vaccine SB MMR (* 'Priorix', SmithKline Beecham, Biologicals) containing the mumps strain, RIT 4385. In this report, the reactogenicity and immunogenicity of SB MMR is compared to a widely used MMR vaccine, Merck MMR (# M-M-R II, Merck and Co Inc) when administered to children aged between 12-24 months of age.

MATERIALS AND METHODS

Study design and participants

The study was conducted at the following study centers in The Philippines: Research Institute for Tropical Medicine, Alabang, Muntinlupa, Holy Child Clinic, Pampanga; Mary Johnston Hospital, Tondo; Capitol Medical Center, Quezon City. Prior to the start of the trial, subject's parents or guardians provided their written informed consent for the study. The study received approval from the Research Institute for Tropical Medicine ERB/IRB and the Bureau of Food and Drugs, Department of Health in Manila, Philippines and was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines.

Subjects and procedures

A total of 700 healthy infants aged between 12-24 months were enrolled in the study. Subjects were randomized in the order in which they enrolled between 4 groups; the first 3 groups received a single dose from consecutive production lots of SB MMR ('Priorix', SmithKline Beecham Biologicals) and the 4th group received a single dose of Merck MMR (M-M-R II, Merck and Co Inc). In the analysis of the data the first three groups was pooled and designated as 'group 1' and then compared to the group receiving Merck MMR, designated as 'group 2' (as described in the statistical analysis section). Data from all subjects was collected for the reactogenicity analysis. A sub-population of 160 subjects were evaluated in the immunogenicity analysis.

Children were excluded from the trial if they had been knowingly exposed to measles, mumps or rubella 30 days prior to the trial or previous history of one or more of these infections; allergy to neomycin and/or egg proteins; upper respiratory tract infection; tuberculosis; history of convulsions (including febrile), epilepsy, or any other CNS disorder. Other exclusion criteria included: administration of parenteral vaccines within 30 days of the start of the trial; immune disorders (including HIV infection); immunosuppressive and immunoglobulin therapy or administration of blood products within 30 days of the start of the trial.

Vaccines

The virus strains and titer for both vaccines are shown in Table 1. The mumps strain RIT 4385 was developed by SmithKline Beecham Biologicals and is derived by limit dilution of a commercial lot of a monovalent mumps vaccine. It has been shown to be a pure clone of the dominant of two virus populations found in the Jeryl Lynn strain source vaccine (Takeuchi *et al*, 1991; Afzal *et al*, 1993). Each vaccine was prepared by reconstituting the freeze dried pellet in 0.5 ml ampoule of water and then injected subcutaneously in the upper left arm.

Reactogenicity assessment

Pain on or within 30 minutes after vaccination (pain on or immediately after injection) was reported by the investigator. Diary cards were used by parents to record solicited local (pain, redness and swelling) adverse experiences on the day of vaccination and 3 subsequent days; and general (fever, rash, parotid gland swelling and signs of suspected meningitis) adverse experiences on the day of vaccination and for 41 subsequent days. The time, onset and duration of symptoms were also recorded. Any redness or swelling was measured, a diameter > 20 mm being defined as severe. Fever was first assessed qualitatively using a temperature sensitive pad. If there was an indication of fever an accurate measurement was made using a thermometer. A rectal temperature > 39.5°C was defined as severe. In cases of parotid swelling, parents were asked to take the child to the investigator and saliva samples were taken. Severe parotid swelling was defined as swelling with additional general symptoms. If signs of suspected meningitis (*eg* vomiting, neck stiffness and photophobia) and/or febrile convulsions were reported, they were followed up by neurological examination according to local medical practice (lumbar puncture was at the investigators discretion). Polymerase chain reaction (PCR) was to be used to detect the mumps virus in saliva samples and cerebrospinal fluid (CSF). All other symptoms or reactions

occurring within 40 days post-vaccination were recorded as unsolicited. The investigator recorded the outcome of all adverse experiences and assessed the relationship of unsolicited symptoms and general reactions to the vaccination.

Immunogenicity assessment

Serum samples taken on the day of vaccination and within 40-63 days post vaccination were stored at -20°C until analysis was performed in a blinded fashion at SmithKline Beecham Biologicals Rixensart, Belgium. All antibody titers were measured using commercial ELISA kits (Enzygnost, Behring). The assay cut-offs were: 150 mIU/ml for measles; 231 U/ml for mumps; and 4 IU/ml for rubella. An antibody titer greater or equal to the cut-off was defined as seropositive. In initially seronegative subjects, seroconversion was defined as the appearance of detectable antibodies levels. Geometric mean titers (GMTs) were calculated.

Statistical analysis

All statistics were performed using SAS with a type 1 error of 5%. The Fisher's exact test was used to compare the incidence of the overall reporting of local and general symptoms between the three groups receiving SB MMR, and if no differences were found the results were pooled. The pooled data for the SB MMR groups (group 1) was then compared to the group receiving Merck MMR (group 2) using the Fisher's exact test. In the same manner, the Fisher's exact test was used to compare the seroconversion rates between groups receiving SB MMR and between the pooled data for SB MMR and Merck MMR. Comparison of mean post-vaccination log titers for seroconverters between groups receiving SB MMR, and between the pooled data for SB MMR and Merck MMR was made using ANOVA one-way.

RESULTS

A total of 700 subjects were enrolled of which 675 completed the trial. Of the subjects who dropped out, 21 were lost to follow-up, two subjects failed to provide a blood sample, one left the study area and the consent of another subject was withdrawn. No subject dropped out due to an adverse event. A total of 686 subjects were included in the reactogenicity analysis. Of the 14 subjects who were eliminated, 6 failed to return either the solicited and unsolicited symptom sheets and 8 only returned the unsolicited symptom sheet. Of the 160 subjects enrolled in the immunogenicity section of the trial, 10 were excluded from the analysis. Two of these subjects were the wrong age and the other 8 subjects failed to comply with the blood sampling schedule. No differences between the three consecutive production lots of SB MMR were observed in terms of reactogenicity or immunogenicity criteria. Hence the pooled data for SB MMR are presented here and referred to as group 1.

Reactogenicity (Table 2)

Fever was the most commonly reported symptom occurring in 31.3% and 35.6% of subjects in groups 1 and 2, respectively. However only 5.9% and 5.2% of subjects, respectively, experienced fever > 39.5°C. In addition, a peak incidence was reported in the second week after vaccination. The reported incidence of rash was 2.7% and 3.4% in groups 1 and 2, respectively, with only 1.0% and 0.6% respectively, of cases been accompanied by fever. There were 4 reports of parotid gland swelling, all in group 1 (0.8%). Two of the severe cases were considered to be related to the vaccination, however the infants made a full recovery without therapeutic intervention. A significantly lower incidence of local injection site reactions, redness ($p < 0.001$) and swelling ($p = 0.003$), was observed in group 1.

There were two reports of convulsions which were found to be related or possibly related to vaccination, however the convulsions occurred on day 3 and 6 post vaccination, respectively. One subjected experience a tonic clonic contraction lasting 3 minutes (related to the vaccination). The other subject experienced a tonic clonic seizure lasting 5 minutes on day 6 after the vaccination (possibly related to the vaccination). All subjects recovered without sequelae.

Immunogenicity

No statistical differences were observed between groups in either seroconversion rates or post-vaccination GMTs (Table 3). All initially seronegative subjects seroconverted with respect to anti-rubella antibodies in both groups. All subjects, except one subject in group 2, were seropositive for anti-measles antibodies post-vaccination. A total of 8/103 and 2/34 subjects in groups 1 and 2 respectively failed to seroconvert with respect to anti-mumps antibodies.

DISCUSSION

Concerns over side effects profile have been

Table 1
Measles, mumps and rubella virus strains and titers of vaccines.

Group 1 - SB MMR		Group 2 - Merck MMR	
strain	* titer ($CCID_{50}$)/dose	strain	* titer ($CCID_{50}$)/dose
Schwarz	$\geq 10^{3.0}$	Edmonston-Enders	$\geq 10^{3.0}$
RIT 4385	$\geq 10^{3.7}$	Jeryl Lynn	$\geq 10^{4.3}$
RA 27/3	$\geq 10^{3.0}$	RA 27/3	$\geq 10^{3.0}$

* Minimum virus titer as stated by manufacturer.

Table 2
The incidence of local and general solicited symptoms.

Symptoms	Groups 1 (N = 512) SB MMR		Group 2 (N = 174) Merck MMR	
	n	%	n	%
Local symptoms				
Pain	14	2.7	8	4.6
severe	1	0.2	0	0.0
Redness *	63	12.3	43	24.9
> 20 mm	5	1.0	13	7.5
Swelling *	22	4.3	19	11.0
> 20 mm	0	0.0	3	1.7
General symptoms				
Fever ≥ 38.1	160	31.3	62	35.6
> 39.5°C	30	5.9	9	5.2
Parotid gland swelling	4	0.8	0	0.0
severe	3	0.6	0	0.0
Rash	14	2.7	6	3.4
rash with fever	5	1.0	1	0.6

N = number of symptom sheets returned.
n = number of symptoms reported (for local reactions); number of subjects with at least one symptom (general reactions)
Severe was defined as preventing normal everyday activities

Fisher's exact test values for the comparison of incidence of symptoms between groups for; redness ($p < 0.001$)*; swelling ($p = 0.003$)*

*statistical significant

one of the major driving forces in vaccine development. The data from this trial shows both vaccines to be well tolerated in a study with a large number of subjects. As mentioned in the introduction, there has been the perceived risk of aseptic meningitis associated with MMR vaccination in the past. However although a risk of aseptic meningitis after MMR vaccination has been estimated to be 1 in 11,000, it has been shown to be dependent on both the methods of surveillance and criteria used to define cases (Miller *et al*, 1993). Due to this low risk of such events, surrogate markers for meningitis have been used. It is thought that febrile convulsions (Miller *et al*, 1993) and cases of fever associated with vomiting (Kimura *et al*, 1996) observed in a 15-35 days of vaccination might represent a milder form of aseptic meningitis. There were no reports of febrile convulsion found to be related to vaccination in this time period. The majority of fever cases (≥ 38.1°C), and cases > 39.5°C, were observed within the first two weeks of vaccination. Fever, and particularly fever > 39.4°C, occurring within this time period has been associated with the measles strain (Markowitz and Katz, 1994). In addition the 2 reports of convulsions which were considered to be related or possibly related to vaccination occurred within the first week after vaccination. Although seizures are known to occur after measles vaccination (ACIP, 1998;

Table 3
Percentage of seroconverted subjects post vaccination and geometric mean titers.

Antibody	Groups 1 N = 111 (SB MMR)			Group 2 N = 38 (Merck MMR)		
	S-	% SC	GMT (95% CI)	S-	% SC	GMT (95% CI)
Anti- measles	88	100.0	2,706.4 (2,410-3,039)	31	96.8	2,878 (2,438-3,397)
Anti- mumps	103	92.2	1,156.6 (973-1,376)	34	94.1	1,384 (1,071-1,788)
Anti- rubella	95	100.0	69.9 (63-78)	35	100.0	74.9 (64.9-86.4)

N = number subjects analyzed
S- = number of initially seronegative subjects
% SC = percentage of seroconverted subject
GMT values are expressed in; mIU/ml for anti-measles; U/ml for anti-mumps; IU/ml for anti-rubella antibodies

Comparison of seroconversion rates between groups for: anti-measles ($p = 0.26$); anti-mumps ($p = 1.00$); anti-rubella ($p = 1.00$)
Comparison of post-vaccination GMTs between groups for: anti-measles ($p = 0.67$), anti-mumps ($p = 0.30$); anti-rubella ($p = 0.51$)

Markowitz and Katz, 1994; Fescharek *et al*, 1990) they are generally thought to occur, as with other measles virus associated adverse reactions, in the 7-10 day period post vaccination. With respect to other vaccine-associated systemic reactions, such as parotid gland swelling and rash accompanied by fever, there was also a low incidence of reporting.

However with respect to fever, a double-blind placebo-controlled MMR trial suggested that the majority of fever was not related to vaccination but was more likely to be a reflection of the relatively high incidence of fever in this age groups (Peltola and Heinonen, 1986). In addition it is then also noteworthy that an incidence of 0.3% febrile convulsions has been observed in an unvaccinated population at this age (Kimura *et al*, 1996).

As mentioned in the introduction, there is a need for high vaccine coverage in order to maintain herd immunity (Anderson and May, 1990) and this can be reduced by poor uptake of the vaccine due to concerns over side-effects (Roberts *et al*, 1995). In addition, sub-optimal uptake of vaccine has been shown to cause a drift of susceptibility to older age groups (Johnson *et al* 1995), for which the associated complications can be more severe. These experiences underline the need for well tolerated vaccines to ensure high compliance, so that the benefits of vaccination can be felt by the population as a whole. In this respect, the excellent tolerability profile of the SB MMR vaccine, which has been demonstrated in an earlier trial (Usonis *et al*, 1998) and recently confirmed in a pooled analysis of data from 8 trials (Usonis *et al*, 1999), will also facilitate uptake.

Equivalent seroconversion rates for all three antibodies were found for both vaccines. The measurement of the antibody response is a surrogate marker for protective efficacy and extensive data exists to demonstrates that seroconversion confers immunity (Peltola *et al*, 1994; Markowitz and Katz, 1994; Cochi *et al*, 1994; Plotkin, 1994; Chen *et al*, 1990; Samb *et al*, 1995; Skendzel 1996; Hilleman *et al*, 1967; Weibel *et al*, 1980; Hilleman *et al*, 1962). The protective levels of antibody for measles and rubella are considered to be > 120 mIU/ml and > 10 IU/ml, respectively (Chen *et al*, 1990; Samb *et al*, 1995; Skendzel, 1996; Hilleman *et al*, 1967; Krugman *et al*, 1965). Although no minimum protective antibody level for mumps has been defined, seroconversion as assessed by a positive antibody titer has been shown to correlate with protection (Cochi *et al*, 1994; Hilleman *et al*, 1962; Miller *et al*, 1995). However the data on the protective efficacy of the MMR vaccine and minimum protective levels have been determined using functional assays, such as the neutralization test and the hemagglutination inhibition test, while a good correlation has been shown between the ELISA and functional assays in other studies (Plotkin, 1994; Sakata *et al*, 1984; Christenson and Bottiger 1990; Pedersen *et al*, 1986; Leinikki *et al*, 1979; Neumann *et al*, 1985; Kleiman *et al*, 1981).

In summary the findings of this trial show that the new SB MMR vaccine was as immunogenic, as the widely used Merck MMR vaccine but showed improved local tolerability. The ready availability of efficacious and safe vaccines is a prerequisite for any successful childhood immunization program. This makes the new MMR vaccine an attractive alternative to healthcare providers.

ACKNOWLEDGEMENTS

The authors would like to thank the following members of the Investigative Team for their efforts towards completing this study: B Quiambo MD, R Capeding MD, L Casidsid RN, V Cabalona RN, T Cedilla, A Dispo MD, B Gopez, A Rago, H Dizon, E Ong MD, J Santos MD, A Koa MD, J Castro RN, K Garcia MD, G Francisco MD, A Libao MD, P Libao and N Barzaga MD (Technical Consultant, Philippine General Hospital). Funding for this study was provided by SmithKline Beecham Biologicals.

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