MMR TRIVALENT VACCINE BASED ON SAFETY, REACTOGENICITY AND IMMUNOGENICITY OBSERVED IN 12–24 MONTH-OLD HEALTHY FILIPINO CHILDREN: EVALUATION OF LOT-TO-LOT CONSISTENCY OF A LIVE-ATTENUATED MEASLES-MUMPS-RUBELLA

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ABSTRACT

In this double-blind, randomized single-dose study, 194 healthy Filipino children aged 12–24 months were randomized into three groups (1:1:1) to receive one of the three lots of live-attenuated measles-mumps-rubella (MMR) vaccine to assess lot-to-lot consistency in safety and immunogenicity. Adverse events were recorded during 43-day post-vaccination follow-up period. Antibody levels were measured using ELISA pre-vaccination and on Day-60. No statistically significant differences were observed across groups for overall incidences of local and general symptoms ($p>0.05$) or immune response rates against the three antigens ($p=0.835$, 0.458 and 0.222 for anti-measles, anti-mumps and anti-rubella, respectively). The three lots demonstrated consistency in their reactogenicity and immunogenicity profile.

INTRODUCTION

Measles, mumps and rubella (MMR) are RNA-viruses that cause highly infectious viral diseases that predominantly affect children worldwide.[1,2] All three diseases can be prevented by existing live-attenuated vaccines.[3] The development of efficacious MMR vaccines and their introduction into the Extended Program of Immunization (EPI) of WHO continues to prevent millions of deaths from measles, mumps and rubella every year.[4] This study aimed to assess the safety, reactogenicity and consistency in immune responses of three manufacturing lots of GlaxoSmithKline Biologicals' MMR vaccine (*Priorix*™) when administered to the study population (healthy Filipino children aged 12–24 months). The study assessed the adverse reactions reported by individual children to the three vaccine lots.

MATERIALS AND METHODS

This double-blind, randomized multi-center study was conducted between February 1997 and May 1997 at five study centers in the Philippines. A total of 194 healthy male and female subjects between 12–24 months of age were enrolled and randomized (using an algorithm of pseudo random numbers given by RS/1 from BBN Inc.) to receive a single dose of one of the three lots of MMR vaccine containing Schwarz measles strain, RIT 4385 mumps strain, and RA 27/3 rubella strain injected subcutaneously in the deltoid. Subjects were excluded if they had a history of or evidence of exposure to measles, mumps and/or rubella vaccination(s) or disease within 30 days prior to participation in the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, after receiving necessary authorization from the Institutional Review Boards. Written informed consent was obtained from the parents/guardians of all subjects prior to enrolment.

Pre-vaccination (Day 0) and post-vaccination (Days 60–70) serum samples were collected to determine antibody titers using commercial ELISA kits (Behring laboratories AG, Marburg, Germany) at GlaxoSmithKline Biologicals' laboratory, Rixensart, Belgium. The serum samples were sent in batches to the laboratory but all testing was done simultaneously. The assay cut-offs were: 150 mIU/mL for measles, 231 U/mL for mumps and 4 IU/mL for rubella. Diary cards were used to record solicited local and general reactions during the four-day (Day 0–3) follow-up period and unsolicited adverse events during the 43-day (Day 0–42) follow-up period; serious adverse events (SAEs) were recorded throughout the study period.

Statistical analyses were performed using Statistical Analysis Software (SAS) version 6.11. Reactogenicity and immunogenicity analyses were performed on the ATP cohort as well as on the intention-to-treat protocol (ITT) cohort. The incidence of local and general symptoms and differences in immune response rates between the three MMR groups were assessed using Fisher's exact test. A subject with antibody titers greater than or equal to the assay cut-off was defined as seropositive, otherwise as seronegative. Comparison of mean post-vaccination log titers for initially seronegative subjects was performed for each antibody titer between the three groups using one-way Analysis of Variance (ANOVA). Immune response was defined as a four-fold or greater increase of a previously positive titer (initially seropositive subjects) or as seroconversion (initially seronegative subjects). Seroconversion rates, seropositivity rates and Geometric Mean Concentrations (GMCs) for measles, mumps and rubella with two-sided 95% confidence intervals (CIs) were calculated for each group.

RESULTS

Demographics

Of the total 194 subjects, 185 completed the study, 193 subjects were included in the overall ATP analysis of reactogenicity, while 180 subjects were included in the overall ATP analysis of immunogenicity. The mean age of subjects was 17 months (standard deviation

[SD]: 3.26 months), the male to female ratio was 1:0.8. In the ATP immunogenicity cohort, statistically significant difference (p=0.045) was observed in the comparison of mean age between Group 1 (16.5 months; SD: 3.03 months) and Group 3 (18.0 months; SD: 3.37 months).

Safety and Reactogenicity

The incidence of all solicited local and general symptoms is presented in Figure 1. Only those subjects whose documented symptom sheets were available for analysis were included in the ATP cohort (193 subjects). The incidences of solicited local and general symptoms were similar across all groups. No statistically significant differences were observed between the groups in the overall reporting of local symptoms (p=0.613) and general symptoms (p=0.577). Redness at injection site was the most commonly reported solicited local symptom. Comparison of the incidences of redness indicated no statistically significant difference between the three groups (p=0.614). Redness was also the most frequently reported Grade 3 local symptom in all groups (Group 1: 3.1%, Group 2: 1.6%, Group 3: 4.7%). Fever (rectal temperature ≥38.1 °C) was the most frequently reported solicited general symptom. Grade 3 fever (rectal temperature >39.5°C) was reported by 9.2%, 6.3% and 4.7% subjects of Group 1, 2 and 3 respectively. The majority of these cases of fever occurred during the second week after vaccination (Group 1: 17 out of 34, Group 2: 10 out of 44, Group 3: 16 out of 31). No statistically significant difference was found in the incidence of fever between the three groups (p=0.405). The majority of the solicited general symptoms reported were found to be unrelated to vaccination (Group 1: 84.8%, Group 2: 68.9%, Group 3: 73.5%).

During the 43-day follow-up, upper respiratory tract infection (Group 1: 52.3%, Group 2: 54.7%, Group 3: 48.4% subjects), cough (Group 1: 44.6%, Group 2: 50%, Group 3: 51.6% subjects) and diarrhea (Group 1: 15.4%, Group 2: 26.6% and Group 3: 12.5% subjects) were the most frequently reported unsolicited symptoms. No statistically significant difference was observed across the groups in terms of incidences of the most frequently reported unsolicited symptoms (p=0.775 for upper respiratory tract infection, p= 0.724 for cough and p= 0.099 for diarrhea). The majority of the unsolicited symptoms were considered unrelated to the vaccination (Group 1: 97.3%, Group 2: 95.8%, Group 3: 99.3%). None of the subjects reported Grade 3 symptoms. All except one symptom (ascaris infestation) was evaluated by the investigator to be causally-unrelated to vaccination.

Two serious adverse events (SAEs) were reported of which one was evaluated by the investigator to be causally related to vaccination. One patient developed fever and cough with rash 10 days post vaccination while the other developed fever and parotid swelling, which was later diagnosed as parotitis. The investigators confirmed that the sequence of symptoms in the second subject was in line with the causal relationship. Both patients recovered completely. No cases of suspected meningism were reported throughout the study.

Immunogenicity

Majority of the subjects across all three groups were seronegative for all three antibodies at study initiation (anti-measles (79.0–83.9%), anti-mumps (90.3–94.6%) and anti-rubella antibodies (91.9–98.4%). No statistically significant differences were observed between groups in the terms of pre-vaccination status for anti-measles (p= 0.838), anti-mumps (p= 0.734) and anti-rubella (p= 0.244) antibodies. The GMCs for all three antibodies, prior to vaccination and at Day 60 for seroconverters, who were initially seronegative, are presented in Figure 2. No statistically significant differences between the three groups were observed in terms of the post-vaccination GMCs for anti-measles, anti-mumps and anti-rubella antibodies in the initially seronegative subjects (p= 0.056, 0.558 and 0.915, respectively).

The majority of the subjects who were initially seronegative had seroconverted by Day 60 (seroconversion— anti-measles: >97.9%, anti-mumps: >93.0%, anti-rubella: 100.0%). The distribution of anti-measles, anti-mumps and anti-rubella antibody titers in initially seronegative subjects was similar in all three groups, at Day 60 (Figure 2). The percentage of the overall immune response for all three antibodies for subjects included in the ATP immunogenicity analysis independent of serostatus showed no statistically significant difference in the overall immune response rates against the three antigens across all groups (p=0.835, 0.458 and 0.222 for anti-measles, anti-mumps and anti-rubella, respectively).

The results of the ITT analyses are in line with that of the ATP analyses (data not shown). No statistically significant differences were detected between the three groups in terms of pre-vaccination antibody status, seroconversion rates and immune response rates.

DISCUSSION

In the present study, no statistically significant differences were observed in the overall incidences of solicited local symptoms (p=0.613) and general symptoms (p=0.577) as well as the most frequently reported unsolicited symptoms (upper respiratory tract infection, cough and diarrhea: p >0.05) between the three groups receiving three different production lots of the MMR vaccine. Two serious adverse events (SAEs) were reported of which one was evaluated by the investigator to be causally related to vaccination. The seroconversion rates and overall immune response rates for the measles, mumps and rubella components of the vaccine were similar for each of the three vaccine groups. For all three vaccine groups, peak incidence of fever was reported in the second week after vaccination, which is in line with published reports from later studies.[4] The incidence of solicited general and local symptoms in this study is also similar to that reported in previously conducted studies. The safety results of this study is similar to studies conducted at a later date in Philippines,[1] Taiwan [5] and other regions like Europe.[6,7] This study formed the basis of the recommendations made for GSK Biologicals' live-attenuated measles-mumps-rubella vaccine *Priorix*™. Results of this study have since been reaffirmed by similar results from lot-to-lot consistency studies conducted in Asia [5]and US [8] at a later date, thus sustaining the relevance of the results of this study conducted back in 1997.

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Conflict of Interest: Dr. Salvacion Gatchalian was employed at the Research Institute for Tropical Medicine at the time of the study conduct where she was the principal investigator on this study. However, she is currently employed at GlaxoSmithKline Biologicals. Htay Htay Han, and Hans L Bock are/were employees of GlaxoSmithKline Biologicals at the time of the study and manuscript preparation. The other authors did not declare any conflicts of interest.

Trademark statement: *Priorix* is a trademark of the GlaxoSmithKline group of companies.

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