Reactogenicity and immunogenicity of a live attenuated tetravalent measles–mumps–rubella–varicella (MMRV) vaccine

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Received 5 October 2001; received in revised form 13 March 2002; accepted 29 August 2002

Abstract

In countries where routine varicella vaccination is implemented, it is usually given at the same age as that recommended for measles–mumps–rubella (MMR) vaccination. A combined multivalent measles–mumps–rubella–varicella (MMRV) vaccine would offer the convenience of a single injection and facilitate implementation of varicella vaccination into routine childhood immunisation schedules. We evaluated the immunogenicity and reactogenicity of a tetravalent MMRV candidate vaccine compared to an extemporaneous mix of a measles–mumps–rubella vaccine and varicella vaccine (MMR/V), and to a measles–mumps–rubella (MMR) vaccine alone. A multicentre study was conducted in which a total of 240 healthy children aged 12 months (80 per group) were randomised to receive MMRV, MMR/V, or MMR alone. Active surveillance for adverse events was undertaken for 43 days post-vaccination. Blood samples were taken prior to vaccination and at 60 days post-vaccination. There were no significant differences between groups in rates of pain, redness, or swelling at the site of vaccination. There was no significant difference in the rate of any fever (axillary temperature ≥37.5 °C) and grade 3 fever (axillary temperature >39.0 °C) between the groups receiving MMRV and MMR during the 43-day follow-up period. Although, a significant increase was found for fever of any cause with onset between days 0 and 14 for MMRV compared to the MMR group, there was no significant difference in grade 3 fever rates during the same period. With respect to immunogenicity, MMRV and MMR/V demonstrated similar seroconversion rates to each component compared to MMR alone, with at least 91.9% of subjects in all groups seroconverting to each vaccine component 60 days after vaccination. Decreased GMTs for varicella antibody at day 60 indicated that there may have been inhibition of this response compared to MMR/V. This tetravalent MMRV candidate vaccine showed promising results, although further examination of the possible increase in minor fever and decreased varicella immunogenicity should be assessed in future studies.

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Keywords: Reactogenicity; Immunogenicity; Measles–mumps–rubella–varicella (MMRV)

1. Introduction

Chickenpox, or primary infection with the varicella-zoster virus (VZV), is a highly contagious disease characterised by fever, malaise, and a generalised vesicular rash. The disease is usually self-limiting, but infants, adolescents, adults, and immunocompromised persons are at higher risk of complications if infected.

Live, attenuated varicella vaccines (derived from the Oka strain) are registered in many countries worldwide, although their routine use is only recommended in some countries, including the United States. Varicella vaccines are usually indicated from the age of 12 months, which is also the age indication for the first dose of combined measles–mumps–rubella (MMR) vaccine [1,2]. Availability of a combined measles–mumps–rubella–varicella (MMRV) vaccine would facilitate the introduction of varicella vaccine into national childhood immunisation schedules without an increase in the required number of injections or visits to the health care provider.

The Scientific Advisory Group of Experts (SAGE) of the World Health Organisation’s Global Program on Vaccination states that “new vaccines should be introduced into national programs in a manner which does not jeopardise current immunisation priorities” [3]. Childhood combination vaccines,
with minimal local and systemic adverse reactions, are more likely to be acceptable to both parents and vaccine providers [4], and may therefore increase compliance with crowded immunisation schedules [5].

Measles–mumps–rubella–varicella combinations have been investigated previously [6–10]. However, an acceptable tetravalent vaccine formulation, in terms of reactogenicity and immunogenicity, is yet to be identified. In this study, we evaluated the safety and immunogenicity of a live attenuated tetravalent MMRV vaccine and an extemporaneous mix of MMR vaccine and varicella vaccine (MMR/V) compared with trivalent MMR vaccine alone.

2. Materials and methods

2.1. Trial design and subjects

This was a single-blind randomised multicentre study with three groups of 80 children enrolled through three Australian tertiary paediatric centres, the Royal Children’s Hospital in Melbourne, the Royal Alexandra Hospital for Children in Sydney, and the Women’s and Children’s Hospital in Adelaide. The study was approved by the respective ethics review committee for each trial centre. Healthy male and female children aged 12 months were enrolled according to a blocked randomisation, six subjects per block in a 2:2:2 ratio. Children in group 1 received the extemporaneous mix of measles–mumps–rubella vaccine and varicella vaccine (MMR/V), while children in group 2 received the combined candidate measles–mumps–rubella–varicella (MMR/V) vaccine, and children in group 3 received measles–mumps–rubella (MMR) vaccine alone.

Children were not enrolled if they had a history of previous measles, mumps, rubella, or varicella infection or vaccination, or if they had been exposed to any of these four diseases within 30 days of trial commencement. They were also ineligible if they had a history of serious chronic illness, major congenital defects, immunosuppression (immunosuppressive illness or therapy), allergic reactions to egg protein or neomycin, allergic or adverse reaction to prior vaccination, convulsions, epilepsy, or other serious nervous system disorder, if they had received any blood products in the prior 3 months, if they had received any parenteral vaccines not included in the study protocol in the prior 30 days, or if they had an acute febrile illness at the planned vaccination time.

After parents or guardians provided written informed consent, the child’s history was documented and a physical examination was conducted by a medical practitioner. Diary cards were distributed to the parents or guardians to record local and systemic reactions, axillary temperature, and other adverse events. Solicited symptoms were recorded on the diary card for 4 days post-vaccination and unsolicited symptoms were monitored for 43 days post-vaccination. Telephone contacts were made by a study nurse weekly until 42 post-vaccination to document adverse events. A final visit including diary card verification and physical examination was performed at 60 days post-vaccination. Any medication received by the child for 30 days prior to study commencement or during the study period was also recorded. Blood samples were taken for antibody estimation prior to vaccination at the first visit and at approximately 60 days (±10 days) after vaccination.

Parents were asked to notify the investigator if any local or general rash/exanthem was observed during the follow-up period. If a rash was vesicular, an attempt was made at collection of vesicular fluid for varicella virus detection and identification by polymerase chain reaction (PCR). Parents were also asked to assess their child for parotid/salivary gland swelling and for any sign/symptom that could be suspected of meningitis from the day of vaccination and continuing once each day for 42 days. If parotid/salivary gland swelling developed or if meningitis was suspected, saliva or cerebrospinal fluid samples were required to be collected in an attempt to verify the presence and identity of mumps virus by PCR.

2.2. Vaccines

All vaccines used in the study were developed and manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. The titres at release of the tetravalent live, attenuated MMRV vaccine and the trivalent MMR vaccine (commercially available as PriorixTM) were $\geq 10^3$ CCID$_{50}$ for Schwarz measles virus strain, $\geq 10^3$ CCID$_{50}$ for RIT 4385 mumps virus strain and $\geq 10^3$ CCID$_{50}$ for RA 27/3 rubella virus strain. Release titres of the tetravalent MMRV vaccine and the varicella vaccine (commercially available as Varilrix™) were $\geq 10^3$ pfu for Oka varicella virus strain. The measles and mumps virus strains were produced on chicken embryo fibroblasts. The rubella and varicella virus strains were produced on human diploid MRC-5 cells.

Vaccines were supplied in monodose vials containing a freeze-dried pellet to be reconstituted with the diluent supplied in a separate pre-filled syringe. All vaccines were stored between 2 and 8°C, and were reconstituted just prior to administration. Participants received a single 0.5 ml dose via subcutaneous injection in the deltoid region of the left arm. All children were observed closely for at least 15 min post-vaccination.

2.3. Laboratory evaluation

Serum titres of IgG antibodies against the vaccine antigen components (anti-measles, anti-mumps, anti-rubella and anti-varicella) were measured before and approximately 60 days after vaccination. The interval between visits 1 and 2 was to be 60 ± 10 days (actual range: 35–77 days). Separated pre- (day 0) and post-vaccination (day 60) serum samples were stored at −20°C until serology was performed at GlaxoSmithKline Biologicals’ laboratory in Rixensart, Belgium. Antibody titres were determined using commercial
assays carried out according to the manufacturer’s instructions. Anti-measles virus IgG, anti-mumps virus IgG, and anti-rubella virus IgG were measured using Enzygnost/Behring immunoassays. The levels used as cut-off points for seropositivity for the antibody assays were: measles ≥ 150 mIU/ml; mumps ≥ 231 U/ml; and rubella ≥ 41 U/ml. Anti-varicella virus IgG was measured using indirect immunofluorescence (Virgo®/Pharmacia), with a cut-off of ≥1:4 dilution.

2.4. Statistical methods

All analyses were carried out on the population adhering to inclusion and exclusion criteria as defined in the protocol, referred to as the according-to-protocol cohort (ATC). Comparison of the overall incidence of symptoms, of local and general symptoms and of each solicited symptom between the three groups were performed using Fisher’s exact test (two-sided comparison of three groups). Fever was defined as axillary temperature ≥37.5°C, and grade 3 fever as axillary temperature >39.0°C.

Seroconversion rates and geometric mean titres (GMTs) of antibodies to measles, mumps, rubella, and varicella, with their 95% confidence intervals (CIs), were calculated for each group at each time point when a blood sample was available. GMTs were calculated by taking the anti-log of the mean of the log transformation of non-zero titres. For GMT calculations, antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off.

Differences in seroconversion rates between groups were computed, with their 90% CI, using an exact method (Proc Binomial, Proc StatXact for SAS Users, Cytel Software Version 3.1). The 90% CI for the GMT ratios were derived from a one-way ANOVA on the log-transformed titres (back-transformation of the 90% CI for the difference in vaccine mean). If the overall test for the null hypothesis of equality between all vaccine groups was rejected, further pairwise comparisons were performed between vaccine groups. The underlying assumptions of normality for the log-transformed titres were evaluated using a Wilk Shapiro test on the residuals of the ANOVA model. Whenever these assumptions were violated a Wilcoxon test was used to compare the antibody titres between vaccine groups.

The equality of variance in log-transformed antibody titres between vaccine groups was evaluated using the Levene test.

3. Results

3.1. Enrolment and attrition

The study was conducted between October 1997 and May 1998. A total of 240 children were enrolled and were randomised for vaccination—80 into each of the three study groups. There were no important differences in baseline demographic characteristics between study group subjects. The mean age of all participants was 12.1 months and 57.9% of children were female. Two participants were lost to follow-up at the final study visit, three subjects received a non-study vaccine during the follow-up period, and parents of two subjects failed to return the diary card, leaving 233 (97.1%) of enrolled children eligible for the ATP analysis of reactogenicity. An additional 12 subjects were excluded from the ATP analysis of immunogenicity leaving 221 (92.1%) evaluable subjects: five subjects had no pre-vaccination blood specimen available for testing; two subjects received corticosteroids during the study period; one subject presented an underlying medical condition (parotitis); three subjects did not comply with the blood sampling schedule; and one subject had mislabelled serology samples.

3.2. Reactogenicity and safety

There was no significant difference between the three groups in the incidence of pain, redness, or swelling at the injection site following vaccination (Table 1). Overall, fever following vaccination was more common in children receiving MMR and V vaccines (MMRV or MMR/V) than in those receiving MMR alone (Table 1 and Fig. 1). However, there was no statistically significant difference (P = 0.067) in the rate of any fever between the MMRV group (70.9%) and the MMR group (55.8%) during the total 43-day follow-up period (Table 1). The same observation was made for the incidence of grade 3 fever, which was 17.7% in the MMRV group compared to 11.7% in the MMR group (P = 0.37). Fever of any cause with onset between days 0 and 14 was significantly more common in MMRV group children (59.5%) compared to the MMR group (41.6%; P = 0.037). However, there was no significant difference in the incidence of grade 3 fever during the same period (10.1% in MMRV and 6.5% in MMR groups; P = 0.56).

Rash was reported in a total of 80 study subjects (Table 2 and Fig. 2). Twelve children had a vesicular or papular/vesicular rash. In general, rash was more frequently observed in subjects vaccinated with MMR/V or MMRV compared to MMR. However, this contrast only reached the threshold of statistical significance for rash reported as suspected or probably related to vaccination (P = 0.051, two-sided Fisher’s exact test between three groups). One subject in the MMR group developed chickenpox 34 days after vaccination. Laboratory tests on vesicular fluid for varicella virus were negative for the vaccine strain, and positive for a wild type strain. One case of parotitis was reported (negative by PCR for mumps virus) and no case of meningitis occurred.

Six serious adverse events were reported in the study. None was deemed related or suspected of being related to the study vaccines, and none caused withdrawal from the study.
Fig. 1. Prevalence of fever (with intensity) over 42 days of follow-up (groups 1–3 from top to bottom: MMR/VMR and MMR). Note: 37.5°C ≤ mild fever; axillary temperature ≤ 38.0°C, 38.0°C < moderate ≤ 39.0°C; severe > 39.0°C.
Table 1
Frequency of solicited symptoms following vaccination

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence and intensity</th>
<th>MMR/V (N = 77)</th>
<th>MMRV (N = 79)</th>
<th>MMR (N = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Pain</td>
<td>Total</td>
<td>12 15.6</td>
<td>9 11.4</td>
<td>6 7.8</td>
</tr>
<tr>
<td></td>
<td>Grade '3' a</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Redness</td>
<td>Total</td>
<td>36 46.8</td>
<td>41 51.9</td>
<td>41 53.2</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mm</td>
<td>3 3.9</td>
<td>3 3.8</td>
<td>3 3.9</td>
</tr>
<tr>
<td>Swelling</td>
<td>Total</td>
<td>16 20.8</td>
<td>14 17.7</td>
<td>9 11.7</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mm</td>
<td>1 1.3</td>
<td>1 1.3</td>
<td>0 0</td>
</tr>
<tr>
<td>Any fever b</td>
<td>Onset ≤ day 2</td>
<td>6 7.8</td>
<td>3 3.8</td>
<td>10 13.0</td>
</tr>
<tr>
<td></td>
<td>Onset ≤ day 7</td>
<td>20 26.0</td>
<td>23 29.1</td>
<td>15 19.5</td>
</tr>
<tr>
<td></td>
<td>Onset ≤ day 14</td>
<td>41 53.2</td>
<td>47 59.5</td>
<td>32 41.6</td>
</tr>
<tr>
<td></td>
<td>Onset ≤ day 42</td>
<td>51 66.2</td>
<td>56 70.9</td>
<td>43 55.8</td>
</tr>
<tr>
<td></td>
<td>SU/PB c</td>
<td>35 45.5</td>
<td>36 45.6</td>
<td>25 32.5</td>
</tr>
<tr>
<td></td>
<td>Grade 3 fever d</td>
<td>8 10.4</td>
<td>8 10.1</td>
<td>5 6.5</td>
</tr>
</tbody>
</table>

MMR/V: extemporaneous mix of MMR and V vaccines; MMRV: tetravalent candidate vaccine; MMR: MMR vaccine alone; N: number of subjects with local solicited symptom sheet (SS) returned; n: number of subjects reporting symptoms with the specific characteristics.

a Pain which prevents normal everyday activities and necessitated medical advice.
b Axillary temperature ≥ 37.5°C.
c Any fever with suspected or probable relationship with vaccination.
d Axillary temperature >39.0°C.

3.3. Immunogenicity

All subjects were initially seronegative for anti-measles antibodies, and all but nine subjects had seroconverted at day 60 (Table 3). The 90% confidence intervals for the difference in seroconversion rates were [−2.5%, 16.8%] for group 2 versus group 1, [−10.4%, 6.9%] for group 3 versus group 2, and [−3.6%, 16.6%] for group 3 versus group 1. At day 60, 90% CI for the GMT ratios were [0.63, 1.14] for group 1 versus group 2, [1.35, 2.46] for group 2 versus group 3, and [1.14, 2.08] for group 1 versus group 3.

All subjects were initially seronegative for anti-mumps antibodies, and at day 60 all subjects but one had seroconverted (Table 3). The 90% confidence intervals for the difference in seroconversion rates were [−5.8%, 13.6%] for group 2 versus group 1, [−7.2%, 10.3%] for group 3 versus group 2, and [−3.9%, 14.8%] for group 3 versus group 1. At day 60, 90% CI for the GMT ratios were [0.76, 1.22] for group 1 versus group 2, [0.82, 1.32] for group 2 versus group 3, and [0.80, 1.27] for group 1 versus group 3.

All subjects were initially seronegative for anti-rubella antibodies, and at day 60 all subjects but one had seroconverted (Table 3). The 90% confidence intervals for the difference in seroconversion rates were [−9.2%, 6.0%] for group 2 versus group 1, [−5.2%, 10.2%] for group 3 versus group 2, and [−7.3%, 6.9%] for group 3 versus group 1. At day 60, 90% CIs for the GMT ratio were [0.91, 1.39] for group 1 versus group 2, [0.58, 0.88] for group 2 versus group 3, and [0.65, 0.99] for group 1 versus group 3.

By day 60 post-vaccination, all subjects initially seronegative in the MMR/V and in the MMRV groups but eight (three in the MMR/V group and five in the MMRV group) had seroconverted for anti-varicella antibodies. The 90% confidence interval for the differences in seroconversion rates was [−13.2%, 7.2%] for group 2 versus group 1. At day 60, the 90% confidence interval for the GMT ratio was [1.25, 2.57] for group 1 versus group 2.

The enhanced measles antibody GMT was not explained by small numbers of outliers skewing the group response. In addition, there was no pattern of systematic non-responder subjects across all antibody groups.
Fig. 2. Rash occurrence over 42 days of follow-up (groups 1–3 from top to bottom: MMR/V, MMRV and MMR).
4. Discussion

With the widespread availability of monovalent varicella vaccines, the possibility exists for greatly enhanced control of chickenpox, and perhaps prevention of herpes zoster (shingles) in later life. However, widespread use of varicella vaccine will substantially depend on its inclusion on national childhood immunisation schedules. Although live, attenuated varicella vaccines (derived from the Oka strain) are available in many countries, universal recommendation of their routine use is not widely implemented. In the United States, a live, attenuated varicella vaccine was licensed in 1995. The Advisory Committee on Immunisation Practices (ACIP) recommended its routine use in July 1996 for all children aged 12–18 months [11]. These recommendations were subsequently expanded in May 1999 to promote wider use of the vaccine in susceptible children and adults [12]. Despite these recommendations, the vaccine coverage in children 19–35 months of age in the United States is overall <70%, which remains substantially lower than that reported for other vaccines administered in the same age range, especially MMR [13]. Among others, potential barriers to varicella vaccination include questions about persistence of immunity and concerns that vaccination of young children will lead to a shift of the disease to older individuals where its consequences are more serious. Another factor to consider is the misconception that varicella is a mild disease. Because the immunisation schedule in the second year of life is crowded, it is possible that priority may be given to vaccines against other diseases perceived as more serious than varicella. Availability of combined measles–mumps–rubella–varicella vaccines may therefore play an important role in increasing compliance with varicella vaccination in countries where the vaccine is already recommended, but also to implement varicella vaccination elsewhere.

Previous reports of combination MMRV vaccines have identified problems with either reactogenicity or immunogenicity of the tetravalent formulation [6–10]. In our study, the immunogenicity of both the tetravalent vaccine and the extemporaneous mix of MMR vaccine and varicella vaccine were encouraging and comparable to the trivalent MMR formulation. At least 91.9% of subjects in each group had seroconverted to each component of the administered vaccines by 60 days following vaccination.

The response to the measles component of the vaccines was similar in terms of proportion of vaccinees who seroconverted, but the extent of the response differed for each group. The tetravalent MMRV and the MMR/V groups exhibited a significantly higher GMT response to the measles component of the vaccine than the MMR group. This enhancement of the measles seroresponse was also observed by White et al. [10] in a study of the Merck MMRV vaccine, where the comparator for MMRV was monovalent varicella vaccine administered contemporaneously but in the other arm, suggesting that the enhancement is a local rather than a generalised phenomenon.

Previous studies have shown a reduced varicella antibody response with combined MMR and varicella vaccination [6–10]. It is still not known what the mechanism is for this interference. Our study did not have a contemporaneous monovalent varicella vaccine group. The varicella antibody GMT in the MMRV group was substantially lower than that of the MMR/V group, although both groups

### Table 3
Seroconversion rates and GMTs for measles, mumps, rubella and varicella at day 60 post-vaccination

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>S+ (n)</th>
<th>S+ (%)</th>
<th>95% CI</th>
<th>GMT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-measles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR/V</td>
<td>74</td>
<td>68</td>
<td>91.9</td>
<td>83.2</td>
<td>97</td>
<td>2509</td>
</tr>
<tr>
<td>MMRV</td>
<td>74</td>
<td>73</td>
<td>98.6</td>
<td>92.7</td>
<td>100</td>
<td>2964</td>
</tr>
<tr>
<td>MMR</td>
<td>72</td>
<td>70</td>
<td>97.2</td>
<td>90.3</td>
<td>99.7</td>
<td>1627</td>
</tr>
<tr>
<td><strong>Anti-mumps</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR/V</td>
<td>73</td>
<td>69</td>
<td>94.5</td>
<td>86.6</td>
<td>98.5</td>
<td>1170</td>
</tr>
<tr>
<td>MMRV</td>
<td>72</td>
<td>70</td>
<td>97.2</td>
<td>90.3</td>
<td>99.7</td>
<td>1212</td>
</tr>
<tr>
<td>MMR</td>
<td>72</td>
<td>71</td>
<td>98.6</td>
<td>92.5</td>
<td>100</td>
<td>1164</td>
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<tr>
<td><strong>Anti-rubella</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR/V</td>
<td>74</td>
<td>74</td>
<td>100</td>
<td>95.1</td>
<td>100</td>
<td>64.5</td>
</tr>
<tr>
<td>MMRV</td>
<td>74</td>
<td>73</td>
<td>98.6</td>
<td>92.7</td>
<td>100</td>
<td>57.3</td>
</tr>
<tr>
<td>MMR</td>
<td>72</td>
<td>72</td>
<td>100</td>
<td>95</td>
<td>100</td>
<td>80.4</td>
</tr>
<tr>
<td><strong>Anti-varicella</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MMR/V</td>
<td>74</td>
<td>71</td>
<td>95.9</td>
<td>88.6</td>
<td>99.2</td>
<td>96.6</td>
</tr>
<tr>
<td>MMRV</td>
<td>73</td>
<td>68</td>
<td>93.2</td>
<td>84.7</td>
<td>97.7</td>
<td>53.9</td>
</tr>
</tbody>
</table>

MMRV/V: extemporaneous mix of MMR and V vaccines; MMRV: tetravalent candidate vaccine; MMR: MMR vaccine alone; N: number of subjects initially seronegative for a given antigen and tested at day 60; S+ (n): number of subjects seropositive at day 60; S+ (%): percentage of subjects seropositive at day 60; LL: lower limit of 95% confidence interval; UL: upper limit of 95% confidence interval; GMT: geometric mean titre calculated on all subjects.
demonstrated similarly high proportions in the seropositive range. Interactions between vaccine components may also be dose dependent. Berger and Just [14] reported that sub-stantially lowering the vaccine concentrations of measles and mumps antigen increased the rates of varicella seroconversion. There also appeared to be a slight attenuation of the rubella seroresponse in both the MMRV and MMR/V groups, although the overall seroconversion rates were very high.

The safety profile of the MMRV vaccine was comparable to that of the MMR/V and MMR groups. The incidence of any fever or fever >39.0°C during the 43-day follow-up period was similar in all groups. Although the incidence of any fever with onset between days 0 and 14 was significantly higher in the MMRV group compared to the MMR group, this effect appeared to be restricted to minor temperature elevation as there was little difference in rates of grade 3 fever during the same period. The minor and non-specific rash excess noted in the MMRV and MMR/V groups, almost of borderline statistical significance, was also reported by White et al. [10]. It is tempting to speculate that this slight elevation of non-specific rash and fever in the 2-week period following vaccination is related to the enhanced measles immune response that appears to be induced by the co-administration of varicella vaccine.

In summary, the findings of this study’s GSK-manufactured vaccine are of particular interest with respect to those reported by White et al. [10] of the Merck MMRV vaccine. In that report, subject numbers in the age range 12–14 months were small and represented only 20% of those studied. Our study confirms their findings of a trend towards an excess of non-specific rash (they found a three-fold higher rate of rash). We also found an enhanced fever response, albeit of a minor nature and certainly within acceptable limits. Although the incidence of fever in the study of White et al. [10] was comparable to the incidence of fever in the MMRV group in the present study, the fever profile as such was neither discussed nor compared to that of MMR alone. In a subsequent study using a modified formulation of the Merck MMRV vaccine with enhanced varicella titre, the rate of fever (oral temperature ≥102°F) was 39.7%, indicating that a balance between acceptable varicella immunogenicity and this systemic response was yet to be defined [15].

Acceptance of multivalent paediatric vaccines requires that the obvious benefits from reducing the number of injections are not offset by a clinically meaningful increase in vaccine reactogenicity or a reduction in the protective efficacy of the vaccine components. The introduction of acellular pertussis vaccines showed that parents, providers, and those who manage national vaccination programs respond favourably to decreased reactogenicity. A combination MMRV product should only be introduced to national immunisation schedules when it is certain that the safety and immunogenicity profiles of the product are comparable to current MMR combinations in use, or that any possible increase in the incidence of an adverse event such as fever would not negatively impact on the current coverage for MMR. The tetravalent formulation studied here shows promise, but further examination of the possible increase in fever and any impact on consumer and provider acceptability needs to be assessed in future research. Parents may be willing to accept a minor increase in the likelihood of mild fever to have their child vaccinated against chickenpox without the need for another injection.

Acknowledgements

The following are gratefully acknowledged for contributing in many ways to this study: Jacqueline Aldis, Dr. Christina Boros, Leonie Dinan, Dr. Raewyn Garin, Dr. Michael Gold, Lindy Harreman, Dr. Helen Marshall, Anna Pisaniello, Dr. Michelle Tilley (Women’s and Children’s Hospital, Adelaide); the many Melbourne Maternal and Child Health Nurses who assisted in subject recruitment, Dr. Anne Altmann, Jennifer Foorid, Rosie Gehrig-Mills, Debbie Gerovich, Dr. Len Hartman, Associate Prof. Geoff Hogg, Dr. Stephen Lambert, Kathleen Lanigan, Charan Sandhu, Dr. Derrick Sim, and Justine McCourt. (Royal Children’s Hospital, Melbourne); Susan Botham, Prof. Margaret Burgess, Barbara Clifton-Smith, Anne-Marie Egan, Dr. Helen Goodwin, Dr. Chamari Kappagoda (Royal Alexandria Hospital for Children, Sydney), Melanie Duiker, Francois Beckers (GlaxoSmithKline Australia and Belgium, respectively). Finally, we would like to thank the many parents who generously assisted us in making this study possible.

References


