

Safety of a 2-dose Regimen of a Combined Measles, Mumps, Rubella and Varicella Live Vaccine Manufactured With Recombinant Human Albumin

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Background: ProQuad, a vaccine containing antigens from M-M-RVAX-PRO (measles, mumps and rubella vaccine) and VARIVAX (varicella vaccine), is indicated for simultaneous vaccination against measles, mumps, rubella and varicella (MMRV) in individuals from 12 months of age. To eliminate blood-derived products of human origin from the manufacturing process of the MMRV vaccine, recombinant human albumin was selected as a replacement for human serum albumin.

Methods: This open-label, multicenter clinical trial (clinicaltrials.gov identifier NCT00560755) was designed to describe the safety profile of a 2-dose schedule of the MMRV vaccine at a 1-month interval in healthy children aged 12–22 months.

Results: In total, 3388 children received at least 1 dose of the MMRV vaccine. Overall, 3376 (99.65%) children were included in the post-dose 1 safety analysis and 3342 (98.64%) in the post-dose 2 safety analysis. After doses 1 and 2, the frequencies of children experiencing solicited injection-site reactions (post-dose 1: erythema 14.31%; swelling 5.57% and pain 10.31%; post-dose 2: erythema 30.46%; swelling 13.23% and pain 11.49%), rashes of interest (post-dose 1: 11.4%; post-dose 2: 2.78%), vaccine-related nonserious systemic adverse events (post-dose 1: 34.86%; post-dose 2: 13.4%) and temperature $\geq 39.4^{\circ}\text{C}$ (post-dose 1: 25.24%; post-dose 2: 12.06%) were consistent with those observed in previous studies of

the MMRV vaccine manufactured with human serum albumin. Neither serious allergic-type adverse events nor anaphylactic reactions were reported.

Conclusion: The results confirm the good safety profiles of MMRV and of measles, mumps and rubella vaccines manufactured with recombinant human albumin.

Key Words: measles, mumps and rubella, varicella, vaccine, ProQuad, recombinant human albumin

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Immunization is widely considered to be one of the greatest success stories of public health policy. It provides an effective means of controlling and potentially eradicating diseases. The World Health Organization immunization campaign from 1967 to 1977 led to the eradication of smallpox, and eradication of poliomyelitis is now considered to be within reach.¹ Worldwide deaths due to measles dropped by almost 40% between 1999 and 2003, and some countries have also set targets for eradicating this disease.¹ Routine vaccination against measles, polio, diphtheria, tetanus, pertussis and tuberculosis is now provided in all developing countries, and a wider range of vaccinations is routinely administered in industrialized nations.¹

The use of combination vaccines minimizes the burden of multiple injections resulting from the recent increases in the number of new vaccines added to the recommended pediatric vaccination schedules in Europe. The advantages of using combination vaccines include fewer injections (which saves time and is less distressing for children and their parents), simplified vaccination schedules, increased compliance, improved vaccination coverage and reduced costs associated with stocking and administering separate vaccines and with extra healthcare visits.^{2–4}

ProQuad (Merck & Co., Inc., Whitehouse Station, NJ) combines antigens from 2 vaccines: measles, mumps and rubella (MMR) vaccine (M-M-RVAXPRO; Merck & Co., Inc.) and varicella vaccine (VARIVAX; Merck & Co., Inc.). Incorporation of MMR and varicella vaccinations into routine pediatric vaccination programs has led to a significant decline in the incidence of the related illnesses and their complications.^{5–9} For example, after the introduction of a nationwide MMR vaccination program in Finland in 1982, measles was eliminated in 1996 and mumps and rubella were eliminated in 1997.⁸ The introduction of the routine use of varicella vaccine in the United States in 1995 resulted in a 75% decrease in the incidence of varicella among children aged 1–4 years between 1992 and 1996 (mean rate of 14.53 cases/1000 person-years) and 2002 (3.67 cases/1000 person-years).⁷ The rationale for adding varicella to the MMR vaccine was to offer a convenient way to implement varicella vaccination while simultaneously achieving high vaccine coverage rates that mirror those of MMR vaccines.

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Results from an extensive clinical development program demonstrated that the combined measles, mumps, rubella and varicella (MMRV) vaccine was as immunogenic as the component vaccines administered separately and is well tolerated in a 1- or 2-dose schedule.¹⁰ The immunogenicity and safety profiles of the MMRV vaccine resulted in recommendations for its use in a 2-dose schedule, with a minimum interval of 1 month between doses, in children from 12 months of age in Europe.

The licensed formulation of the MMRV vaccine is manufactured with human serum albumin (HSA), as a component of the viral growth medium. However, recombinant human albumin (rHA) is being investigated as an alternative in line with recommendations from the European Medicines Agency to eliminate blood-derived products of human origin from vaccine manufacturing processes.^{11,12} rHA is structurally and analytically comparable with unmodified monomeric HSA, and experimental data confirmed that the substitution of HSA by rHA in viral growth media results in satisfactory vaccine virus growth and product characteristics. Thus, rHA and HSA are considered functionally comparable for the production of viral bulk preparations.¹³

It has been shown that the substitution of HSA by rHA during the manufacturing process of the MMR vaccine did not affect its safety profile when given as a 1-dose regimen from 12 months of age.¹⁴ This led to the marketing authorization of M-M-RVAXPRO in Europe in 2006. Since then, >40 million doses of the MMR vaccine manufactured with rHA have been distributed worldwide, and postmarketing surveillance data support its good safety profile. According to the recommendations, the second dose of a MMR vaccine can be administered several months to several years after the first dose. This poses problems for the assessment of the safety of a 2-dose routine vaccination schedule in an observational study. The objective of this clinical study was to provide further safety data on a 2-dose regimen of a rHA-manufactured vaccine given within a short interval.

This European multicenter clinical trial was specifically designed to describe the safety profile of a 2-dose schedule of the MMRV vaccine at a 1-month interval in healthy children in their second year of life and consequently to confirm that the safety profile was not affected by the substitution of HSA by rHA.

MATERIALS AND METHODS

Study Design

This open-label, descriptive, single-arm, multicenter study was conducted at 86 centers (84 of which enrolled participants) in 7 European countries (Denmark, Germany, Greece, Italy, The Netherlands, Spain and Sweden) between October 2007 and November 2008 (NCT00560755).

The primary objective was to describe the safety profile of the second dose of the MMRV vaccine manufactured with rHA. The secondary objective was to describe the safety profile of the first dose of the MMRV vaccine manufactured with rHA. No immunogenicity assessments were planned in the study.

The tolerability of repeated doses of rHA-manufactured vaccines was of interest for public health bodies, so the study design was discussed and endorsed by the Committee for Medicinal Products for Human Use. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki from the World Medical Association¹⁵ as well as relevant national and local requirements. Written informed consent was obtained from the parent(s) or legal guardian before study entry.

Study Participants

Healthy children aged 12–22 months at the first vaccination were eligible for inclusion in the study. Children were excluded if they had a vaccination history and/or suspected clinical history and/or exposure in the past 30 days to measles, mumps, rubella and/or varicella virus. Children were also excluded if any of the following applied: febrile illness (defined as rectal temperature $\geq 38.0^{\circ}\text{C}$) in the past 3 days; history of encephalopathy, seizure disorder or progressive, evolving or unstable neurological condition; known sensitivity and/or allergy to any component of the study vaccine; impairment of the immune system (including receipt of systemic corticosteroids for >14 days); receipt of inactivated vaccine in the past 14 days or live vaccine in the past 28 days. In addition, children with chronic severe disease or other medical condition, receiving treatment or with a medical history that, in the opinion of the investigator, could interfere with the immune response and/or evaluation of the study objectives were also excluded.

The second vaccination was postponed in cases of raised rectal temperature ($\geq 38.0^{\circ}\text{C}$), immunosuppressive therapy, a recent tuberculin test or administration of a nonstudy vaccine in the previous 28 days.

Withdrawals were allowed at the request of the parent(s) or legal guardian or if, in the investigator's opinion, further participation in the study would have been detrimental to the child's well-being. In these instances, further follow-up of the child was used to establish if the reason for withdrawal was an adverse event.

Vaccine Administration

Enrolled children received a dose of the MMRV vaccine administered subcutaneously in the deltoid region at visits 1 and 2. Dose 1 (visit 1) was administered between 12 months and 22 months of age and dose 2 (visit 2) between 28 days and 42 days after dose 1. The second dose was administered in the contralateral arm to that used for the first dose.

Safety Assessments

Safety criteria were assessed after the second dose of the MMRV vaccine (primary objective) and after the first dose of the MMRV vaccine (secondary objective). After administration of each dose, solicited injection-site reactions (erythema, swelling and pain) were recorded between day 0 (day of vaccination) and day 4. Unsolicited injection-site reactions and systemic adverse events, in particular rashes of interest (those resembling measles, rubella, varicella or zoster) and mumps-like illness, were recorded between day 0 and day 28 after administration of each dose. Diagnosis of mumps or mumps-like illness, measles or measles-like rash, rubella or rubella-like rash, varicella or varicella-like rash and zoster or zoster-like rash was made on the basis of clinical descriptions provided by the parents and/or clinical evaluation by the investigator. Virological confirmation was not performed. Body temperature was measured if the child appeared feverish. Measurements of rectal temperature were encouraged, but axillary measurements of temperature were permitted. For the analysis of temperature values, axillary values were converted to the rectal equivalent by adding $+0.9^{\circ}\text{C}$. Serious adverse events (defined as untoward medical occurrences that resulted in death, or were life-threatening, or required hospitalization, or resulted in persistent/significant disability/incapacity, or were other important medical events) were recorded from the time of signing the consent form until the last visit for each child.

Adverse events (defined as any untoward medical occurrence in a patient or clinical trial subject administered an investigational medical product and which did not necessarily have a causal relationship with the product) were recorded on diary cards by the

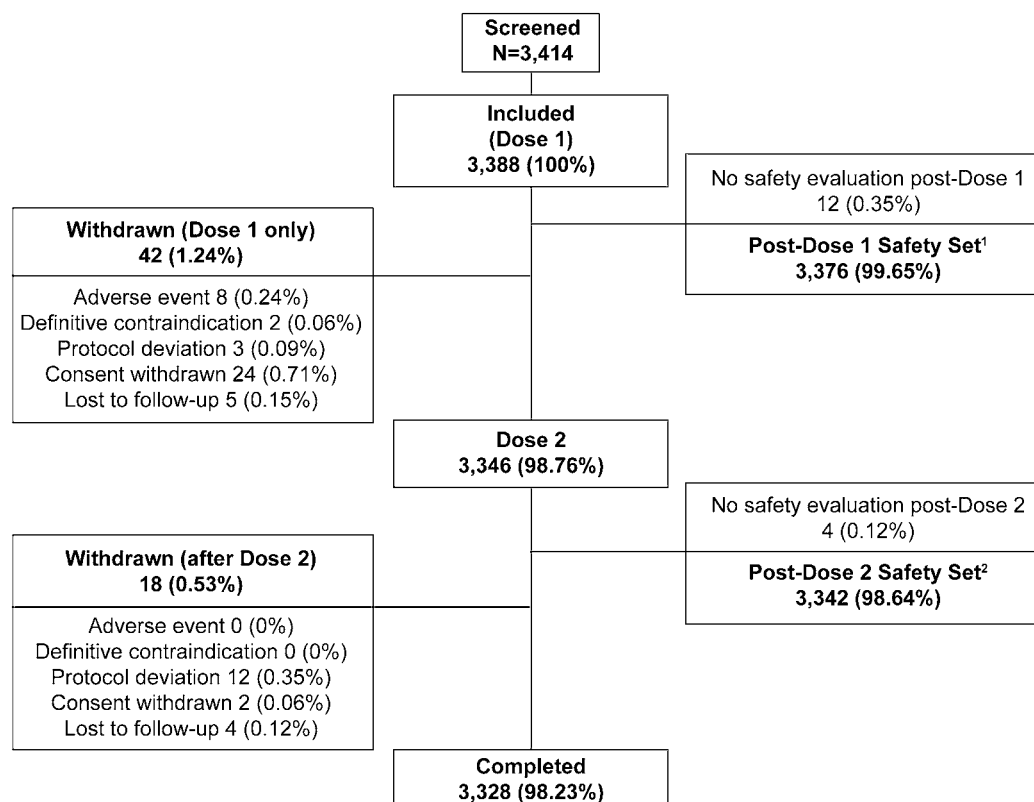


FIGURE 1. Participation of children throughout the study. Data presented as n (%); percentages calculated based on the number of included children; ¹children who received dose 1 of the MMRV vaccine and who had safety follow-up data after the first administration; ²children who received 2 doses of the MMRV vaccine and who had safety follow-up data after the second administration.

child's parent(s) or legal guardian. A diary card was completed after each dose of the MMRV vaccine and was reviewed by the investigator at the next visit.

Statistical Analyses

Determination of Sample Size. The plan was to include 3340 children in the study which, assuming a maximum rate of 10% of nonevaluable children (children without safety follow-up after the second dose of the MMRV vaccine), would result in approximately 3000 children contributing to the safety analysis for the primary objective. Among 3000 children, the probability of observing at least 1 specific event after the second dose of the MMRV vaccine would be $\geq 95\%$ if the true rate of the event was at least 1 event in 1000 children. Furthermore, there would be 97.5% confidence that the true incidence rate was $< 1/1000$ for events not observed after the second dose of the MMRV vaccine.

Safety Analyses. All data were presented using descriptive statistics. No formal statistical hypotheses were tested for primary or secondary objectives. The number of events, and the number and proportion of children affected, was calculated after each dose for the defined safety parameters. Two-sided 95% confidence intervals were provided for proportions and are based on the exact method for binary variables.¹⁶ The analysis of safety was undertaken on the safety set for each dose. The post-dose 1 safety set was defined as all children who received the first dose of the MMRV vaccine and who had follow-up safety data. The post-dose 2 safety set was defined as all children who received 2 doses of the MMRV vaccine and who had post-dose 2 follow-up safety data.

RESULTS

Study Population

In total, 3388 children received at least 1 dose of the MMRV vaccine (Fig. 1). Of these, the mean age at the time of the first dose of the MMRV vaccine was 14.6 months [standard deviation (SD), 2.3; range, 11.5–23.8 months] and the mean age at the time of the second dose of the MMRV vaccine was 15.7 months (SD, 2.3; range, 12.9–25.1 months). There were 1650 (48.70%) girls and 1738 (51.30%) boys, whose mean weight was 10.4 kg (SD, 1.4; range, 7–17 kg) and mean height was 78.3 cm (SD, 4.0; range, 67–97 cm).

Safety Evaluation

Overall, 3376 (99.65%) children were included in the post-dose 1 safety analysis and 3342 (98.64%) were included in the post-dose 2 safety analysis.

Safety After the First Dose of the MMRV Vaccine (Secondary Objective). Adverse events occurring after the first dose of the MMRV vaccine are detailed in Table 1. From day 0 to day 28 after dose 1, 26.27% of children experienced at least 1 injection-site reaction. Solicited injection-site reactions occurring between day 0 and day 4 after dose 1 were reported in 21.42% of children and included erythema (14.31%), swelling (5.57%) and pain (10.31%). Overall, 64.10% experienced at least 1 systemic adverse event including 34.86% of children who experienced a systemic adverse event assessed by the investigator to be related to the study vaccine. There were 11.40% of children reporting a rash of interest (those resembling measles, rubella, varicella or zoster) and 7 (0.21%) children with mumps-like illness from day 0 to day 28 after dose 1 of MMRV vaccine.

TABLE 1. Adverse Events and Temperature Measurements After a First Dose Of the MMRV Vaccine (Secondary Objective); Number and Percentage of Children and 2-Sided 95% CI in the Post-dose Safety Set (N = 3376) With an Adverse Event Between Day 0 (Day of Vaccination) and Day 28

	n (%)	[95% CI]
Adverse events from day 0 to day 28	2418 (71.62)	[70.07–73.14]
Vaccine-related adverse event from day 0 to day 28	1709 (50.62)	[48.92–52.32]
Injection-site reaction from day 0 to day 28	887 (26.27)	[24.80–27.79]
Solicited injection-site reaction from day 0 to day 4	723 (21.42)	[20.04–22.84]
Injection-site erythema	483 (14.31)	[13.14–15.53]
Injection-site swelling	188 (5.57)	[4.82–6.40]
Injection-site pain	348 (10.31)	[9.30–11.38]
Unsolicited injection-site reaction from day 0 to day 28	251 (7.43)	[6.57–8.37]
Systemic adverse event from day 0 to day 28	2164 (64.10)	[62.45–65.72]
Vaccine-related systemic adverse event from day 0 to day 28	1177 (34.86)	[33.26–36.50]
Injection-site rash of interest from day 0 to day 28	16* (0.47)	[0.27–0.77]
Noninjection-site rash of interest from day 0 to day 28	385 (11.40)	[10.35–12.52]
Measles/measles-like rash	233† (6.90)	[6.07–7.81]
Rubella/rubella-like rash	98‡ (2.90)	[2.36–3.53]
Varicella/varicella-like rash	71§ (2.10)	[1.65–2.65]
Zoster/zoster-like rash	1¶ (0.03)	[0.00–0.16]
Mumps/mumps-like illness from day 0 to day 28	7 (0.21)	[0.08–0.43]
At least 1 rectal (or equivalent) temperature from day 0 to day 28 $\geq 38.0^{\circ}\text{C}$	1894 (56.10)	[54.41–57.78]
At least 1 rectal (or equivalent) temperature from day 0 to day 28 $\geq 39.4^{\circ}\text{C}$	852 (25.24)	[23.78–26.74]
Serious adverse event**	40 (1.18)	[0.85–1.61]
Vaccine-related serious adverse event**	15 (0.44)	[0.25–0.73]
Withdrawal for adverse event**	8 (0.24)	[0.10–0.47]
Withdrawal for vaccine-related adverse event**	6 (0.18)	[0.07–0.39]
Withdrawal for vaccine-related serious adverse event**	3 (0.09)	[0.02–0.26]
Withdrawal for vaccine-related nonserious adverse event**	3 (0.09)	[0.02–0.26]

*Including 3 cases of measles-like rash, 2 cases of rubella-like rash and 11 cases of varicella-like rash.

†Including 1 case of suspicion of measles.

‡Including 2 cases of suspicion of rubella.

§Including 6 cases of suspicion of varicella

¶No cases of suspicion of zoster.

||No cases of suspicion of mumps.

**From visit 1 to visit 2.

CI indicates confidence interval.

In addition to the adverse events presented in Table 1, 56.10% of children had a rectal temperature $\geq 38.0^{\circ}\text{C}$, including 25.24% having a rectal temperature $\geq 39.4^{\circ}\text{C}$ after dose 1. Of these, most children experienced their highest body temperature between day 5 and day 11 postvaccination (Fig. 2).

After dose 1, 40 (1.18%) children had 45 serious adverse events. Seventeen serious events considered by the investigator to be vaccine-related were reported in 15 children, including febrile seizure (7 children), febrile seizure associated with pyrexia (temperature at 39.2°C ; 1 child), loss of consciousness [assessed as a suspected unexpected serious adverse reaction (SUSAR) in 1 child], pneumonia (assessed as SUSAR in 1 child who experienced 2 episodes), acute tonsillitis (1 child), gastroenteritis (1 child), viral infection (1 child), asthma (1 child) and rash (1 child). The 8 vaccine-related febrile seizures occurred between 3 days and 25 days after the first dose and, in all cases except 1, the child had an associated medical condition (febrile infection, upper respiratory infection, herpangina, gastroenteritis, pharyngitis, viral disease and nasopharyngitis, in 1 child each). The loss of consciousness occurred in 1 child 10 days after receiving the first dose of the MMRV vaccine, was of short duration and resolved spontaneously before being seen by a physician. The child was not withdrawn from the study and received the second dose of the MMRV vaccine without experiencing a further serious adverse event. The episodes of pneumonia occurred in the context of nonserious gastroenteritis in a child with a history of asthma, repetitive broncho-obstructive episodes and bronchospasm episodes. The child developed fever and ear suppuration 3 days after receiving the first dose and was treated with amoxicillin plus clavulanic acid. Ten days later, he was

hospitalized with pneumonia and received further antibiotic treatment (cefuroxime). Three weeks later, he was hospitalized with bilateral pneumonia, which resolved with further antibiotic treatment.

Nonserious allergic-type adverse events were recorded in 21 (0.62%) children after dose 1, including 5 children with adverse events considered to be vaccine-related according to the investigator: urticaria (2 children), dermatitis allergic (2 children) and pruritus (1 child). No serious allergic-type adverse events or anaphylactic reactions were recorded after the first dose of the MMRV vaccine.

Eight (0.24%) children were withdrawn from the study due to an adverse event occurring after dose 1. Among the 6 withdrawals who were considered to be vaccine-related, 3 were nonserious (dermatitis allergic, rubelliform rash and erythema multiforme minor) and 3 were serious [febrile seizure, pneumonia (SUSAR) and asthma].

Safety After a Second Dose of the MMRV Vaccine (Primary Objective). Adverse events occurring after the second dose of the MMRV vaccine are detailed in Table 2. From day 0 to day 28 after dose 2, 34.23% of children experienced at least 1 injection-site reaction. Solicited injection-site reactions occurring between day 0 and day 4 after dose 2 were reported in 33.72% of children and included erythema (30.46%), swelling (13.23%) and pain (11.49%). Overall, 40.42% experienced at least 1 systemic adverse event, including 13.44% of children who experienced a systemic adverse event assessed by the investigator to be related to the study vaccine. There were 93 (2.78%) children reporting a rash of interest (those resembling measles, rubella, varicella or zoster) and 1

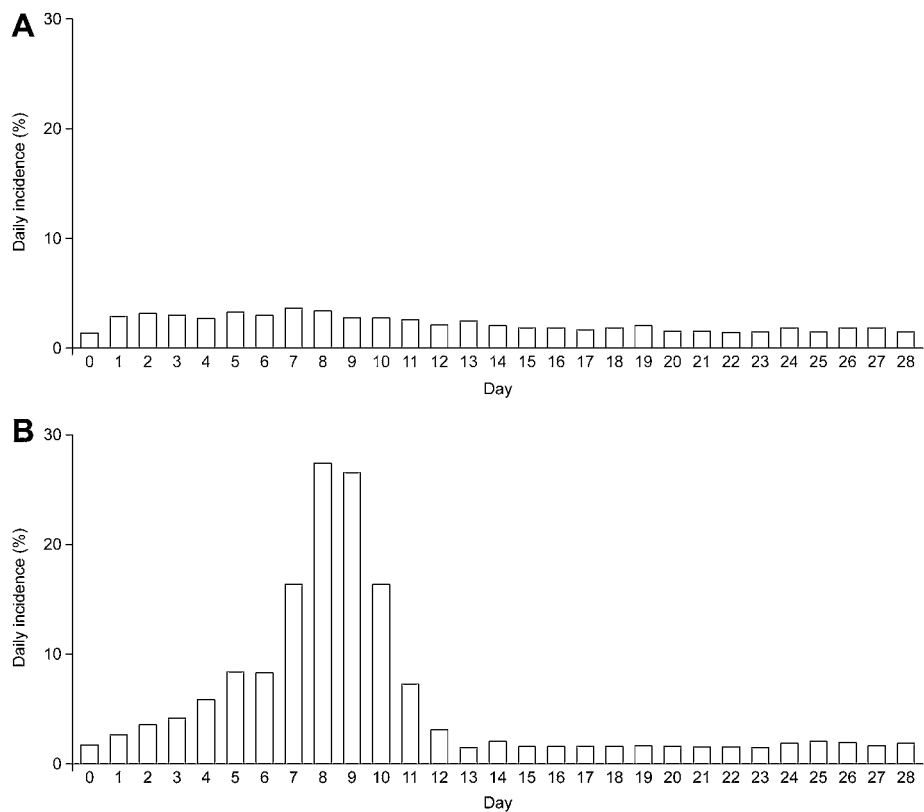


FIGURE 2. Daily incidences of rectal temperature ≥38.0°C for post-dose 1 (A) and post-dose 2 (B) safety sets.

TABLE 2. Adverse Events and Temperature Measurements After a Second Dose of the MMRV Vaccine (Primary Objective); Number and Percentage of Children and 2-Sided 95% CI in the Post-dose 2 Safety Set (N = 3342) With an Adverse Event Between Day 0 (Day of Vaccination) and Day 28

	n (%)	[95% CI]
Adverse events from day 0 to day 28	1927 (57.66)	[55.96–59.34]
Vaccine-related adverse event from day 0 to day 28	1396 (41.77)	[40.09–43.47]
Injection-site reaction from day 0 to day 28	1144 (34.23)	[32.62–35.87]
Solicited injection-site reaction from day 0 to day 4	1127 (33.72)	[32.12–35.35]
Injection-site erythema	1018 (30.46)	[28.90–32.05]
Injection-site swelling	442 (13.23)	[12.09–14.42]
Injection-site pain	384 (11.49)	[10.43–12.62]
Unsolicited injection-site reaction from day 0 to day 28	55 (1.65)	[1.24–2.14]
Systemic adverse event from day 0 to day 28	1351 (40.42)	[38.76–42.11]
Vaccine-related systemic adverse event from day 0 to day 28	449 (13.44)	[12.30–14.64]
Injection-site rash of interest from day 0 to day 28	1* (0.03)	[0.00–0.17]
Noninjection-site rash of interest from day 0 to day 28	93 (2.78)	[2.25–3.40]
Measles/measles-like rash	54† (1.62)	[1.22–2.10]
Rubella/rubella-like rash	19‡ (0.57)	[0.34–0.89]
Varicella/varicella-like rash	21§ (0.63)	[0.39–0.96]
Zoster/zoster-like rash	1¶ (0.03)	[0.00–0.17]
Mumps/mumps-like illness from day 0 to day 28	1 (0.03)	[0.00–0.17]
At least 1 rectal (or equivalent) temperature from day 0 to day 28 ≥38.0°C	873 (26.12)	[24.64–27.65]
At least 1 rectal (or equivalent) temperature from day 0 to day 28 ≥39.4°C	403 (12.06)	[10.97–13.21]
Serious adverse event**	22 (0.66)	[0.41–0.99]
Vaccine-related serious adverse event**	7 (0.21)	[0.08–0.43]

Dose 2 was administered between 28 days and 42 days after dose 1.
*One case of varicella-like rash.
†No cases of suspicion of measles.
‡No cases of suspicion of rubella.
§Including 1 case of suspicion of varicella.
¶No cases of suspicion of zoster.
||No cases of suspicion of mumps.
**From visit 2 to visit 3.
CI indicates confidence interval.

(0.03%) child with mumps-like illness from day 0 to day 28 after dose 2 of the MMRV vaccine.

In addition to the adverse events presented in Table 2, 26.12% of children had a rectal temperature $\geq 38.0^{\circ}\text{C}$, including 12.06% who had a temperature $\geq 39.4^{\circ}\text{C}$ after dose 2. The distribution of days on which children experienced their highest body temperature throughout the 28-day follow-up period after dose 2 was almost uniform (Fig. 2).

A total of 25 serious adverse events were observed in 22 children (0.66%) after dose 2. In total, 7 serious adverse events considered by the investigator to be vaccine-related were recorded: febrile seizure (4 children), central cyanosis (assessed as a suspected SUSAR in 1 child), pyrexia (associated with nonvaccine-related serious upper respiratory tract infection and vaccine-related febrile convulsion in 1 child) and bronchitis (1 child). The 4 vaccine-related febrile seizures occurred between 6 days and 23 days after dose 2, and in all cases the children had a concomitant infectious disease (respiratory tract infection in 1 child; tonsillitis in 1 child; nasopharyngitis in 2 children). The cyanosis occurred 9 days after vaccination in the context of a nonserious gastroenteritis, was of short duration and resolved spontaneously. The child was admitted to hospital as a consequence of the cyanosis, but no specific diagnosis could be established. Breathing and blood gas analysis were without abnormalities; urine and stool analyses were normal; and the child's electrocardiogram showed no pathological findings. Although the investigator assessed the cyanosis as being possibly related to the MMRV vaccine, concomitant gastroenteritis was suggested as an alternative explanation.

Nonserious allergic-type adverse events were recorded in 16 (0.48%) children after dose 2 and 5 of these adverse events were vaccine-related according to the investigator: urticaria (2 children), drug hypersensitivity (1 child), dermatitis allergic (1 child) and pruritus (1 child). No serious allergic-type adverse events, anaphylactic reactions or adverse events leading to withdrawal were recorded after dose 2.

DISCUSSION

In the present study, the safety of a 2-dose schedule of MMRV vaccine manufactured with rHA was assessed in healthy children. The study findings raised no safety concerns with this formulation compared with earlier studies performed with the MMRV vaccine manufactured with HSA.

Three serious adverse events were recorded as SUSARs during the study, which, in the opinion of the investigators, were possibly related to the study vaccine. Each of these SUSARs (cyanosis, loss of consciousness and pneumonia) occurred in 3 individual children. Cyanosis (reported after dose 2) and loss of consciousness (reported after dose 1) were events of short duration that resolved spontaneously. The pneumonia (reported after dose 1) occurred in a child with a history of asthma, repetitive broncho-obstructive episodes and bronchospasm episodes.

The safety profile of the first dose of the MMRV vaccine manufactured with rHA was similar for the frequency and types of adverse events with the safety data for the MMRV vaccine manufactured with HSA reported from 5 controlled clinical trials¹⁰ and as described in the European Summary of Product Characteristics,¹⁷ including injection-site reactions, elevated temperature, allergic-type adverse events and febrile seizures.

Of the 5 nonserious allergic-type adverse events considered to be vaccine-related after dose 1 of the MMRV vaccine, only 1 (severe allergic dermatitis) led to the child's withdrawal from the study. A second dose of the study vaccine was administered to the

other 4 children without further allergic-type reactions. It is therefore unlikely that the events experienced by these 4 children were vaccine-related, allergic-type events.

The elevated temperatures recorded in the present study were as expected, with a lower incidence after dose 2 compared with that seen after dose 1. The expected frequency of fever $\geq 39.4^{\circ}\text{C}$ rectal-equivalent (which equates to an oral temperature of approximately 38.9°C) after the MMRV vaccination is $\geq 10\%$.¹⁷ In the present study, the timing of the elevated temperatures after dose 1 (Fig. 2) suggests that they could be related to the peak time of replication of the live vaccine viruses included in the MMRV vaccine, specifically of the measles component, whereas the occurrence of raised temperature up to 28 days after dose 2 suggests that the fever was less likely to be vaccine-related. The percentage of children with a temperature $\geq 39.4^{\circ}\text{C}$ following the first dose (25.24%) was higher in the present study than in a separate study in which infants received the vaccine at 9, 11 and 12 months (8.8%, 10.3% and 14.8% of children, respectively).¹⁸ The reasons underlying this difference are not clear, but may reflect the safety focus of the present study, which could increase reporting of safety findings. In addition, considerable country-specific variation is observed in the reporting of safety findings. Therefore, between-study comparisons should be done cautiously.

In 11 of the 12 cases of vaccine-related febrile seizure observed in the present study (after doses 1 and 2), a concomitant infectious disease was recorded by the investigator, which could provide an alternative etiology for the febrile seizures. Febrile seizure is an uncommon vaccine-related adverse event after the administration of the MMRV vaccine, occurring with an expected frequency of 0.1–1% after dose 1.¹⁷

An analysis of a postmarketing observational safety study in children receiving their first dose of the MMRV vaccine ($N = 31,298$, 99% vaccinated in their second year of life) showed that 0.14% of children experienced febrile seizures within 30 days of vaccination.¹⁹ The postmarketing results cannot be directly compared with those from the present study because the methodology and objectives of the studies were different. Active safety monitoring in the current study may have led to a higher incidence of febrile seizures being reported. After dose 1 of the MMRV vaccine, the timing of febrile seizures (whether or not considered as vaccine-related by the investigator) was similar in both studies; 4 of the 10 cases in the present study versus 22 of the 44 in the postmarketing observational study occurring between 5 days and 12 days after vaccination.¹⁷ This is consistent with data from other clinical trials and another postmarketing study that observed an elevation in febrile seizures 7–10 days after vaccination among 12- to 23-month-old children.^{10,20,21} The results of the postmarketing study indicated that, among children aged 12–23 months receiving their first dose of MMRV vaccine during their second year of life ($N = 83,107$), one additional febrile seizure occurred after vaccination per 2300 who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit.²¹ In a separate study evaluating the immunogenicity, tolerability and safety of a 2-dose schedule of the MMRV vaccine (manufactured with rHA) in healthy children from 9 months of age, no vaccine-related febrile seizures were recorded in 1483 children receiving at least 1 dose of the MMRV vaccine.¹⁸ Taken together, these findings add to the body of data supporting that the MMRV vaccine manufactured with rHA is associated with only a low likelihood of febrile seizures.

In conclusion, the safety of the MMRV vaccine manufactured with rHA is consistent with the safety profile of the MMRV vaccine manufactured with HSA in previous studies. The results of

the present study support the good safety profiles of MMRV and MMR vaccines manufactured with rHA.

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