Review

Immunogenicity and safety of a measles–mumps–rubella–varicella vaccine following a 4-week or a 12-month interval between two doses

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Abstract

Background: The MMRV combination vaccine, Priorix-Tetra™, is currently licensed in several European countries using a two-dose schedule in infants aged ≥ 9 months, with a preferred 6-week to 3-month interval between doses. This study was undertaken to generate safety and immunogenicity data for two doses of MMRV vaccine administered according to dose schedules using the shortest permitted interval of 4 weeks versus a longer interval of 12 months, which would allow flexible adaptation to local immunization calendars.

Methods: Healthy children aged 11–13 months were randomized (1:1:1) to receive 2 doses of either: MMRV vaccine with a 4-week interval between doses (MMRV-4W group, N = 188), MMRV vaccine with a 12-month interval between doses (MMRV-12M group, N = 184), or MMR vaccine with a 4-week interval between doses (MMR group, N = 187). Blood samples were taken prior to, and 4–6 weeks after each vaccination.

Results: Post-Dose 2, both MMRV groups exhibited an adequate immunogenic response for all components; however the MMRV-12M group showed significantly greater geometric mean titers for mumps, rubella and varicella. Two varicella breakthrough cases occurred within the 12-month interval between doses in the MMRV-12M group. Local and general reactogenicity results were similar for all groups except for the MMRV-4W group, which had a greater incidence of fever during Days 0–14 post-Dose 1.

Conclusions: Two doses of MMRV vaccine administered in the second year of life elicited adequate immunogenicity and were well-tolerated whether administered with a dose interval of 4 weeks or 12 months.

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1. Introduction

Measles, mumps, rubella and varicella represent a significant healthcare burden, even in developed countries, despite the availability of effective and well-tolerated vaccines to prevent them. Measles and varicella can be fatal, even in previously healthy individuals [1–5]. Rubella infection during early pregnancy can result in fetal death and frequently causes congenital rubella syndrome [6]. Mumps can cause serious complications such as meningitis and encephalitis [7]. The measles–mumps–rubella–varicella (MMRV) combination vaccine, Priorix-Tetra™ developed by GSK Biologicals, has been licensed in many countries and is currently available in Belgium, Luxembourg, Cyprus, Czech Republic, Germany, Greece, Israel, Italy, Malta, Netherlands, Slovakia, Slovenia and Switzerland. Previous studies have shown that the MMRV vaccine is as immunogenic and well tolerated as separate measles–mumps–rubella (MMR) and varicella vaccines [8–11]. Similar data are also available for another MMRV vaccine, ProQuad™ [12]. Combination vaccines have been shown to offer several benefits including a reduced overall number of injections per subject, simplified vaccination schedules and increased compliance, which can therefore also be expected for the present vaccine [13].

It is widely acknowledged that a two dose MMR vaccination schedule is necessary to prevent outbreaks and similarly, a two dose schedule has also been recommended for varicella vaccination [14–18]. In countries where a second dose of MMR is implemented, it is given at 4–6 years of age or 10–12 years of age. However vaccination coverage has been inadequate, especially for the second dose where >80% coverage is required for herd immunity [19]. As a consequence, repeated measles, mumps and rubella outbreaks have occurred in several EU countries [16]. The WHO now allows a shortening of the MMR schedule, depending on the local grammatic and epidemiological situation, with a minimum MMR dose interval of 1 month [7]. Germany, Austria, France, the Czech Republic and Switzerland have moved the second dose into the second year of life as this is expected to improve coverage [20]. A shorter schedule would also maximize the benefits of a second dose against varicella, as the likelihood of breakthrough cases increases with time since administration of a first dose. However, longer schedules may have benefits in terms of compliance in countries where a later second dose fits with current vaccination schedules.

Priorix-Tetra™ is licensed in several European countries for use according to a two-dose schedule in infants aged ≥9 months, with a 6-week to 3-month dose interval. While this preferred interval was established in several studies [8,10,11] a 4-week minimum dose interval is recommended by the Centers for Disease Control and Prevention (CDC) for subsequent administration of live viral vaccines [21,22].

Given the benefits of providing the second dose in the second year of life and the trend to implement such a schedule, this study aimed to evaluate the extreme dose intervals within this schedule. The first dose of MMRV vaccine was administered to children aged 11–13 months and the second dose was administered 4 weeks or 12 months later.

### Table 1

<table>
<thead>
<tr>
<th>Virus strain</th>
<th>MMRV vaccine</th>
<th>MMR vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwarz measles</td>
<td>≥10³⁰ CCID₅₀</td>
<td>≥10¹⁶ CCID₅₀</td>
</tr>
<tr>
<td>Jeryl Lynn-derived mumps RIT 4385 strain</td>
<td>≥10³⁰ CCID₅₀</td>
<td>≥10¹⁶ CCID₅₀</td>
</tr>
<tr>
<td>Wistar RA 27/3 rubella</td>
<td>≥10¹⁰ plaque forming units</td>
<td>≥10¹⁰ CCID₅₀</td>
</tr>
<tr>
<td>Oka varicella virus</td>
<td>≥10¹⁰ CCID₅₀</td>
<td>NA</td>
</tr>
</tbody>
</table>

The MMRV vaccine and MMR vaccine both came from single batch.

2. Methods

The study was performed between 23 November 2005 and 23 May 2007. Forty-two centers participated in the study (39 in Germany, 2 in Belgium and 1 in the Netherlands), and recruited 385 subjects in Germany, 44 subjects in Belgium and 130 subjects in the Netherlands. The study was performed in accordance with International Committee on Harmonization (ICH) good clinical practice guidelines and the Declaration of Helsinki. The study was approved by local institutional review boards and each child’s parent/guardian provided written informed consent.

2.1. Study design and subjects

Healthy children were eligible for this phase III study if aged between 11 and 13 months at the time of first vaccination, and not previously immunized with MMR or MMRV. The children were randomized (1:1:1) into three parallel treatment groups: MMRV 4-week dose interval group (MMRV-4W), MMRV 12-month dose interval group (MMRV-12M) and MMR vaccine (control group) (Fig. 1). We evaluated the immune response elicited by a two dose schedule of MMRV vaccine given at 4 week and 12 month intervals, and a two dose schedule of MMR vaccine with a 4-week interval. Antibody persistence, one year after Dose 2 was also evaluated in the MMRV-4W and MMR vaccine groups. All groups received two doses of vaccine, subcutaneously, in the upper left arm (deltoid region). The study was open labeled between the MMRV-4W group and the MMR-12M group. However, a single-blind applied for the MMRV-4W group and MMR group until Week 10.

2.2. Investigated vaccines

GSK Biologicals developed and manufactured the MMRV and MMR vaccines which were supplied as lyophilized pellets in monodose vials for delivery of 0.5 ml after reconstitution with the supplied water for injection (see Table 1 for composition details).

2.3. Variables measured/assessed

2.3.1. Immunogenicity variables

IgG antibody levels were measured in a blinded manner using commercial ELISA (Enzygnost™, Dade Behring, Marburg, Germany) immunoassays for measles (cut-off 150 mIU/mL), mumps (231 U/mL) and rubella (4 IU/mL) (Fig. 1). Antibody levels
against varicella were measured using IFA (Virgo™, Hemagen Diagnostics, Columbia, MD, with modifications), a commercial indirect immunofluorescence assay (cut-off 4 dilution⁻¹). IFA was chosen as it has been shown to be a sensitive and specific alternative to ELISA[23,24], and to the gold standard FAMA[23]. Seropositivity was defined as IgG antibody titers ≥ cut-off at a given time point. Seroconversion was defined as the appearance of IgG antibodies (i.e. antibody titer ≥ cut-off value) in the serum of subjects who were seronegative before vaccination.

2.3.2. Safety variables

Solicited local and general symptoms were recorded by parents/guardians on diary cards after each dose. Local symptoms (injection site pain, redness and swelling) were recorded from Days 0 to 3; general symptoms (fever, rash, parotitis/salivary gland swelling, signs of meningism) from Days 0 to 42, except after the first dose in MMRV-4W and MMR groups, in which they were recorded from Day 0 to Days 28–30.

Symptoms were defined as ‘related’ if there was a reasonable possibility that the vaccine contributed to the adverse event. Breakthrough was defined as physician-confirmed varicella disease occurring >42 days post-vaccination in both MMRV groups (not in the MMR group).

2.4. Statistics

The total vaccinated cohort was analyzed for safety and the according-to-protocol (ATP) cohort was analyzed for immunogenicity. The total vaccinated cohort included subjects who received at least one dose of study vaccine. The ATP cohort included subjects who had post-Dose 2 serology data for at least one vaccine component and excluded subjects who did not comply with study procedures (interval between visits, received supplementary doses) or who had breakthrough cases.

No formal statistical comparison was planned or performed. In total, 540 subjects were to be enrolled to ensure that at least 450 subjects (150 in each group) were included in the ATP cohort for the analysis of the primary endpoint, which assessed the seroconversion rates in the MMRV-4W group and the MMRV-12M group, 42–56 days after the second dose. Statistical analyses were performed using Statistical Analysis Systems (SAS) version 9.1 (including Proc-StatXact-5 module for SAS users from Cytel). Seroconversion rates and geometric mean titers (GMTs) with 95% CIs were calculated for antibodies against each vaccine component. The 95% CIs for percentages and GMTs within each group were calculated assuming independence between doses, and overlapping 95% CIs were used to suggest similarity between groups [25]. The 95% CIs for GMTs were calculated by exponential transformation of the 95% CI for the mean of log-transformed titer, and any antibody titers below the assay cut-off were given an arbitrary value of half the cut-off value. The study was designed, and the data collected and analyzed, by GSK Biologicals in coordination with the authors.

3. Results

3.1. Study population

Subject disposition is shown in Fig. 2. The ATP cohort included 359 subjects: 110 subjects in the MMRV-4W group, 142 subjects in the MMRV-12M group and 107 subjects in the MMR group. The total vaccinated cohort included 279 males and 280 females who were mainly Caucasian (92%) with a mean age (SD) of 12.0 (0.86) months at time of inclusion in the study (Table 2). Treatment groups were comparable for age, gender and race. The reasons for exclusion from the ATP cohort are presented in Table 2.

The most common reasons were non-compliance, either with the interval of 28–30 days between the two doses in the MMRV-4W and MMR groups or with the blood sampling schedule. The demographic characteristics of the ATP cohort were similar to those of the total vaccinated cohort (Table 3).

3.2. Immunogenicity

Prior to vaccination, ≤2.2% of subjects in the total vaccinated cohort were seropositive for measles, mumps or rubella antibodies, and varicella baseline seropositivity rates were 6.5% and 8.1% in the MMRV-4W and MMRV-12M groups, respectively.

Four weeks after Dose 1 in the MMRV-4W group, seroconversion for mumps was 71.3% while the other components ranged from 97.2% to 98.9%, and the MMR group showed similar seroconversion rates for mumps, measles and rubella (Table 4). Six weeks after Dose 1 in the MMRV-12M group, the seroconversion rates for
**Fig. 2.** Subject disposition of total vaccinated cohort.

### Table 2
Demography (total vaccinated cohort).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MMRV-4W, N = 188</th>
<th>MMRV-12M, N = 184</th>
<th>MMR, N = 187</th>
<th>Total, N = 559</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months) Mean ± SD</td>
<td>12.0 ± 0.83</td>
<td>12.0 ± 0.84</td>
<td>12.1 ± 0.90</td>
<td>12.0 ± 0.86</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>92 (48.9)</td>
<td>96 (52.2)</td>
<td>92 (49.2)</td>
<td>280 (50.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>96 (51.1)</td>
<td>88 (47.8)</td>
<td>95 (50.8)</td>
<td>279 (49.9)</td>
</tr>
</tbody>
</table>

N = total number of subjects; n (%) = number (percentage of subjects in a given category); SD, standard deviation.

### Table 3
Subjects excluded from ATP cohort and reasons for exclusion.

<table>
<thead>
<tr>
<th>Reason for exclusion from the ATP cohort</th>
<th>MMRV-4W, N = 188</th>
<th>MMRV-12M, N = 184</th>
<th>MMR, N = 187</th>
<th>Total, N = 559</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of vaccine(s) forbidden</td>
<td>1 (0.5)</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Interval between doses in the MMRV-4W</td>
<td>25 (13.3)</td>
<td>0</td>
<td>32 (17.1)</td>
<td>57 (10.2)</td>
</tr>
<tr>
<td>and MMR groups outside 28–30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria violation</td>
<td>0</td>
<td>0</td>
<td>3 (1.6)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Initially seropositive or initially</td>
<td>4 (2.1)</td>
<td>3 (1.6)</td>
<td>5 (2.7)</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>unknown antibody status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying medical condition forbidden</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>by the protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-compliance with blood sampling</td>
<td>10 (5.3)</td>
<td>0</td>
<td>5 (2.7)</td>
<td>15 (2.7)</td>
</tr>
<tr>
<td>schedule (including wrong and unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dates)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>25</td>
<td>5</td>
<td>31</td>
<td>61</td>
</tr>
<tr>
<td>Month 13.5</td>
<td>39</td>
<td>29</td>
<td>40</td>
<td>108</td>
</tr>
<tr>
<td>Essential serological data missing</td>
<td>10 (5.3)</td>
<td>0</td>
<td>5 (2.7)</td>
<td>15 (2.7)</td>
</tr>
<tr>
<td>Obvious incoherence or abnormality or</td>
<td>5 (2.7)</td>
<td>5 (2.7)</td>
<td>2 (1.1)</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>error in data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject with breakthrough case of</td>
<td>0</td>
<td>2 (1.1)</td>
<td>0</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>measles, mumps, rubella and/or varicella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP immunogenicity cohort</td>
<td>110 (58.5)</td>
<td>142 (77.2)</td>
<td>107 (57.2)</td>
<td>359 (64.2)</td>
</tr>
</tbody>
</table>

N = number of subjects in the total vaccinated cohort.

† Subjects may have been excluded from the ATP cohort for more than one reason and therefore can be counted more than once in the table.

‡ Non-compliance is subdivided according to the schedule of blood sample collection for each subject group. Month 3 includes non-compliance to blood sampling at visits 1–3 for MMRV–4W or MMR–4W and visits 1–2 for MMRV–12M, Month 13.5 includes non-compliance at visit 4 for MMRV–4W or MMR–4W and visits 3–4 for MMRV–12M.
all components were high (94.0–98.4%) and antibodies persisted to give similarly high seroconversion rates 1 year after Dose 1. The immunogenicity results of the total vaccinated cohort were consistent with those of the ATP cohort (data not shown).

Seroconversion rates for each vaccine component were within the same range in all treatment groups 6 weeks after Dose 2 (Table 4). However, GMTs for all vaccine components tended to be higher than in the MMR group. The anti-measles GMT, 12 months after the second dose when administered at Month 12, was also higher in the MMRV-4W group than the MMR group. Antibody persistence one year after Dose 2 was consistent with those of the ATP cohort (data not shown).

The immunogenicity results of the total vaccinated cohort were tend to give similarly high seroconversion rates 1 year after Dose 1. All components were high (94.0–98.4%) and antibodies persisted to give similarly high seroconversion rates 1 year after Dose 1. The immunogenicity results of the total vaccinated cohort were consistent with those of the ATP cohort (data not shown).

Seroconversion rates for each vaccine component were within the same range in all treatment groups 6 weeks after Dose 2 (Table 4). However, GMTs for all vaccine components tended to be higher than in the MMR group. The anti-measles GMT, 6 weeks post-Dose 2, was also higher in the MMRV-4W group than the MMR group. Antibody persistence one year after Dose 2 was consistent with those of the ATP cohort (data not shown).

3.2.1. Disease contact and breakthrough cases (total vaccinated cohort)

During the follow-up year, no contact with mumps was reported in any group, one contact with measles was reported in the MMRV-12M group and one contact with rubella was reported in the MMR group. Multiple subjects reported having at least one contact with varicella: 20 in the MMRV-4W group (10.8% of subjects) and 28 in the MMRV-12M group (15.2% of subjects). Varicella contact was not analyzed in the MMR group. Two physician-confirmed cases of varicella breakthrough were reported in the MMRV-12M group at 9 and 10 months after Dose 1 (each within 13 days of contact with varicella). No other breakthrough cases were reported.

5.3. Safety and reactogenicity

The incidences of pain, redness and swelling were similar in all treatment groups after both the first and the second dose. Clinically significant solicited local injection site symptoms were very rare (<2% of subjects in any treatment group had a grade 3 event after either dose) (Table 5). The incidence of injection site pain was lower after Dose 2 compared with Dose 1 while the incidence and intensity of redness and swelling remained similar after each dose. The MMRV-4W group had a higher observed incidence of fever of any intensity for Days 0–14 after both Dose 1 and Dose 2 than the MMRV-12M group and the MMR group (Table 6). Daily prevalence of fever of any intensity after Dose 1 peaked between Days 7 and 11 in all groups (Fig. 3). No peak in prevalence was observed after a second dose of either MMR or MMRV irrespective of the interval between the two doses. The incidence of fever ≥39.5 °C, related fever, related fever ≥39.5 °C, and fever requiring medical assistance were within the same range in all three treatment groups during Days 0–14 and Days 0–42. The incidence of fever in all groups tended to be lower after Dose 2 than after Dose 1. Measles/rubella-like rash was reported in one subject in each group after Dose 1 and
in one subject in the MMR group after Dose 2. Varicella-like rash was reported in one subject in each of the MMRV groups and five subjects in the MMR group after Dose 1 and in four subjects in the MMR group after Dose 2. There were four events of febrile convulsions during the study: two subjects in the MMRV-12M group, 36 days and 265 days after Dose 1, and two subjects in the MMR group, one 27 days after Dose 1 and one 18 days after Dose 2. Twenty-six serious adverse events (SAEs) were reported in twenty-two subjects during the study. No event was determined by the investigator to be vaccine-related. All subjects recovered without sequelae.

4. Discussion

In Europe, the recommended schedule for Priorix-Tetra™ is two doses given to infants aged ≥9 months with a dose interval of between 6 weeks and 3 months. The minimum permitted interval is 4 weeks, which applies to all live attenuated vaccines and is based upon a single study by the CDC [21]. Prior to our study, no clinical trial data had been published where subsequent doses of an MMRV combination vaccine were administered at such a short interval.

After two doses of the MMRV vaccine administered with a 4-week interval, the immunogenic response was found to be adequate without any safety or reactogenicity issues. Two doses of MMRV vaccine administered with a 12-month interval were also well tolerated and provided high seropositivity rates which ranged from 95.2 to 100%, 6 weeks after Dose 2. The immunogenicity results after two doses of vaccine in both MMRV groups were within the ranges reported in MMRV vaccine literature [8–11,15]. As in previous studies, higher GMTs were obtained following MMRV vaccination compared to MMR vaccination [8–11]. Immunogenicity after Dose 2 in the short interval groups, MMRV-4W and MMR, was

### Table 5

Incidence of solicited local symptoms reported during the 4-day (Days 0–3) post-vaccination period following each dose (total vaccinated cohort).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MMRV-4W (N = 182)</th>
<th>MMRV-12M (N = 176)</th>
<th>MMR (N = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (% (95% CI))</td>
<td>n (% (95% CI))</td>
<td>n (% (95% CI))</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21 (11.5 (7.3, 17.1))</td>
<td>31 (17.6 (12.3, 24.1))</td>
<td>21 (11.4 (7.2, 16.9))</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0 (0.0 (0, 2.0))</td>
<td>1 (0.6 (0, 3.1))</td>
<td>0 (0.0 (0, 2.0))</td>
</tr>
<tr>
<td>Redness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>1 (0.5 (0, 3.0))</td>
<td>0 (0.0 (0, 2.1))</td>
<td>1 (0.5 (0, 3))</td>
</tr>
<tr>
<td>Swelling (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>0 (0.0 (0, 2.0))</td>
<td>0 (0.0 (0, 2.1))</td>
<td>0 (0.0 (0, 2.0))</td>
</tr>
</tbody>
</table>

N = number of subjects with at least one documented dose, n/% = number/percentage of subjects reporting at least once the symptom. 95% CI = exact 95% confidence interval.

### Table 6

Incidence of solicited fever reported during Days 0–14 and Days 0–42 following each dose (total vaccinated cohort).

<table>
<thead>
<tr>
<th>Fever parameter</th>
<th>MMRV-4W group</th>
<th>MMRV-12M group</th>
<th>MMR group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
</tbody>
</table>

Fever reported Days 0–14

Post Dose 1

- Any
  - >39.5 °C
  - Related
  - Medical advice

Post Dose 2

- Any
  - >39.5 °C
  - Related
  - Medical advice

Fever reported Days 0–42

Post Dose 1

- Any
  - >39.5 °C
  - Related
  - Medical advice

Post Dose 2

- Any
  - >39.5 °C
  - Related
  - Medical advice

N = number of subjects with at least one documented dose, n/% = number/percentage of subjects reporting at least once the symptom.

*In the MMRV-4W and MMR groups with the second dose administered 4 weeks after the first, maximum follow-up after the first dose was 28–30 days (Days 0–28). In the MMRV-12M group, follow-up after the first dose was 43 days (Days 0–42). Follow-up after the second dose in all three groups was 43 days (Days 0–42).
not adversely affected by the fact that the immune response to Dose 1 was incomplete when the second dose was administered. Despite low eligibility for the ATP cohort, the immunogenicity results were consistent in analyses of both the ATP cohort and the total vaccinated cohort. The stringent windows for dose administration and blood sampling were responsible for the low inclusion rate in the ATP cohort, but were a necessary condition to obtain a cohort suitable for evaluation of short interval as a primary objective of the study.

The seroconversion rate for mumps was 71% in the MMRV-4W group versus 94% in the MMRV-12M group and the GMTs for mumps, measles and rubella tended to be lower in the MMRV-4W group. These apparent differences can be explained by the sampling time point, i.e. 4 weeks post-Dose 1 in the MMRV-4W and MMR groups, and 6 weeks in the MMRV-12M group. A delayed immune response seems plausible for a live vaccine and our findings illustrate that the response to measles, mumps and rubella is incomplete at only 4 weeks after vaccination [26]. However the absence of such a difference for the varicella component was less expected. Due to the delay in response, blood samples are typically taken at 6–12 weeks after administration for this type of vaccine.

The occurrence of breakthrough cases following varicella vaccines is well-known, especially in children vaccinated with a single dose [27–29]. Time since vaccination has also been previously identified as a risk factor for developing breakthrough disease. While a two-dose schedule has been proposed to address the former, a shorter interval between doses would minimize the latter, which was illustrated by the occurrence of two breakthrough cases in the interval between doses in the MMRV-12M group. In comparison, the MMRV-4W group had no breakthrough cases despite a similar rate of varicella contact. In addition to being more flexible, a longer interval between doses, such as 12 months, may result in better long term antibody persistence. This is particularly relevant for mumps and varicella as immunity provided by these components is known to wane over time [30–33].

The incidence of local symptoms, fever and rash in the MMRV groups was similar to previous studies of MMRV vaccine [9,15,34,35]. We found a greater incidence of fever after the first dose of MMRV-4W compared to the MMR vaccine, but the incidence of fever for each treatment after Dose 2 was similar, which matches previous results [35]. It is of interest to note that we observed a higher incidence of fever 0–14 days after Dose 1 in the MMRV-4W group than both the MMRV-12M and MMR groups, in which the incidence of fever was similar. One possible explanation for this apparent discrepancy is that fever incidence is multifactorial and that high variability of fever incidence may occur irrespective of the vaccine administered.

Four cases of febrile convulsion were reported during this study, but none were considered related to the vaccine. Febrile convulsion was not observed during the 5–12 days after vaccination, when the risk is reported to be at its highest (relative risk of 2.20, Day 5–12 post-Dose 1) and a potential concern related to MMRV vaccination [36].

The majority of the data on the present vaccine were generated using a two-dose schedule, with a 6 or 12-week interval [8,10,11]. Our study confirms that two doses provide adequate immunogenicity with an acceptable reactogenicity profile when administered at the shortest feasible interval for live viral vaccines of 4 weeks. However, considering the apparent incompleteness of the immune response at the time Dose 2 is administered in this schedule, the more widely studied interval of 6 weeks or longer should probably remain the preferred option, whenever feasible. The vaccine also showed itself to be highly immunogenic and well-tolerated when given with a 12-months dose interval. Our findings show the flexibility of this vaccine to be accommodated in increasingly crowded childhood vaccination calendars, but also illustrate that the prevention of early breakthrough cases is an important consideration in vaccination calendars.

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Fig. 3. Prevalence of solicited fever by day (Days 0–28) after Dose 1 (total vaccinated cohort).
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