



One or two doses of live varicella virus-containing vaccines: Efficacy, persistence of immune responses, and safety six years after administration in healthy children during their second year of life [☆]

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ABSTRACT

Background: This phase III B follow-up of an initial multicenter study (NCT00226499) will evaluate the ten-year efficacy of two doses of the combined measles-mumps-rubella-varicella vaccine (MMRV) and one dose of the live attenuated varicella vaccine (V) versus a measles-mumps-rubella control group (MMR) for the prevention of clinical varicella disease. Here we present efficacy results for six years post-vaccination.

Methods: In phase A of the study, healthy children aged 12–22 months from ten European countries were randomized (3:3:1) and received either two doses of MMRV, or one dose of combined MMR and one dose of monovalent varicella vaccine (MMR+V), or two doses of the MMR vaccine (control), 42 days apart. Vaccine efficacy against all and against moderate or severe varicella (confirmed by detection of viral DNA or epidemiological link) was assessed from six weeks up to six years post-dose 2 for the MMRV and MMR+V groups, and was calculated with 95% confidence intervals (CI). The severity of varicella was calculated using the modified Vázquez scale (mild ≤ 7 ; moderately severe = 8–15; severe ≥ 16). Herpes zoster cases were also recorded.

Results: 5289 children (MMRV = 2279, mean age = 14.2, standard deviation [SD] = 2.5; MMR+V = 2266, mean age = 14.2, SD = 2.4; MMR = 744, mean age = 14.2, SD = 2.5 months) were included in the efficacy cohort. 815 varicella cases were confirmed. Efficacy of two doses of MMRV against all and against moderate or severe varicella was 95.0% (95% CI: 93.6–96.2) and 99.0% (95% CI: 97.7–99.6), respectively. Efficacy of one dose of varicella vaccine against all and against moderate or severe varicella was 67.0% (95% CI: 61.8–71.4) and 90.3% (95% CI: 86.9–92.8), respectively. There were four confirmed herpes zoster cases (MMR+V = 2, MMR = 2), all were mild and three tested positive for the wild-type virus.

Abbreviations: VZV, varicella-zoster virus; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; CI, confidence interval; SAE, serious adverse event; HZ, herpes zoster; VE, vaccine efficacy; ATP, according-to-protocol; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction; IDMC, Independent Data Monitoring Committee; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; TVC, total vaccinated cohort; HR, hazard ratio; LL, lower limit; UL, upper limit.

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Conclusions: Two doses of the MMRV vaccine and one dose of the varicella vaccine remain efficacious through six years post-vaccination.

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1. Introduction

Varicella (chickenpox), caused by the varicella-zoster virus (VZV), is a highly contagious vaccine-preventable disease, responsible for 4.2 million hospitalizations and 4200 deaths annually, worldwide [1]. In countries where universal vaccination was introduced, the incidence of varicella cases, including hospitalizations and deaths, has substantially declined [2–5].

An important aspect in the design of universal immunization programs against varicella is the number of doses. While one-dose schedules were shown to be effective against the disease, breakthrough cases were still reported [2–6]. Out of the 33 countries that recommended varicella containing vaccines, 14 recommended a two-dose schedule. Another important aspect is the choice of vaccine, i.e. monovalent or combined varicella vaccine. Improved uptake rates might be achieved by the co-administration of varicella-containing vaccines with routine childhood vaccines or with the use of combined varicella-containing vaccines [7].

GSK's trivalent measles-mumps-rubella vaccine (MMR; *Priorix*) and the monovalent live attenuated varicella vaccine (V; *Varilrix*) are licensed in many countries worldwide. Both vaccines are indicated for active immunization of children at least 9 months of age, and can be given concomitantly, but at separate injection sites [8,9].

GSK has developed a combined tetravalent measles-mumps-rubella-varicella vaccine (MMRV; *Priorix-Tetra*) that offers convenience for parents and medical practitioners by combining the benefits of measles-mumps-rubella and varicella vaccination in a single injection, and would therefore improve the vaccine coverage both against chickenpox and against measles, mumps and rubella. Moreover, meningococcal vaccines could be co-administered with MMRV at the same clinical visit [10]. The immunogenicity and safety of the combined MMRV have been demonstrated in clinical trials; MMRV was licensed based on comparative immunogenicity trials versus monovalent varicella vaccines [11–13].

Phase A of this phase III, observer-blinded, randomized, controlled, multicenter study (NCT00226499) assessed protection against varicella in naive children who received two doses of MMRV or one dose of monovalent varicella vaccine at 12–22 months of age. After a mean follow-up of approximately three years, efficacy of two doses of MMRV against all varicella was 94.9% (97.5% confidence interval [CI]: 92.4–96.6), and against moderate to severe varicella was 99.5% (97.5% CI: 97.5–99.9). Efficacy of one-dose varicella vaccine was 65.4% (97.5% CI: 57.2–72.1) against all varicella and 90.7% (97.5% CI: 85.9–93.9) against moderate to severe varicella [14].

We report the efficacy, antibody persistence and safety data up to six years after the second vaccine dose. Long term follow-up is ongoing and will extend up to ten years post-vaccination.

2. Methods

2.1. Study design and participants

The study design was previously described [14]. Briefly, this study is a follow-up of the phase A, observer-blind, controlled, study conducted in Czech Republic, Greece, Italy, Lithuania, Nor-

way, Poland, Romania, Russian Federation, Slovakia and Sweden between 2009 and 2015, in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines [15,16]. The study protocol was reviewed and approved by independent ethics committees. Protocol deviations were presented elsewhere [14].

In phase A of the study, healthy children aged 12–22 months from the ten countries mentioned above were randomized (3:3:1) to one of the three treatment groups, and received either two doses of MMRV (*Priorix-Tetra*, GSK) at Day 0 and Day 42 (MMRV group), or one dose of MMR (*Priorix*, GSK) at Day 0 and one dose of monovalent varicella vaccine (*Varilrix*, GSK) at Day 42 (MMR+V group), or two doses of the MMR (*Priorix*, GSK) vaccine (control) at Day 0 and Day 42 (MMR group).

Study population (with inclusion and exclusion criteria), randomization and blinding, as well as vaccine composition and administration route, were previously described [14].

For phase B, the study remained observer-blind for all groups with the exception of the MMR+V group in countries where the national vaccination schedules included a second dose of MMR vaccination at 4–8 years of age (Italy, Lithuania, Romania, Russian Federation, Sweden). Independent Data Monitoring Committee (IDMC) members also remained blinded to the study treatment group when assessing varicella cases.

The objectives of this phase B study were secondary and descriptive, i.e. to assess: the long-term efficacy of one dose of monovalent varicella vaccine or two doses of MMRV in preventing probable and confirmed varicella cases after vaccination, the efficacy of the study vaccines according to the severity of varicella cases and the occurrence of complicated varicella cases reported as serious adverse events (SAEs) (efficacy objectives). The varicella immune response in terms of varicella seropositivity rates and geometric mean antibody concentrations (GMCs) in all children four and six years post-vaccination (immunogenicity objectives) were also assessed. The safety of the study vaccines was evaluated in terms of occurrence of SAEs and by description of occurred herpes zoster (HZ) cases, in all children following vaccination (safety objectives).

The current analysis was designed to monitor the severity of varicella in vaccinated and unvaccinated children, and to determine whether or not susceptible individuals remained in the control group and to assess the benefit of two doses or one dose of varicella vaccination versus control.

2.2. Efficacy assessment

The main analysis of vaccine efficacy (VE) was based on the according-to-protocol (ATP) cohort for efficacy in phase A + B and children were followed up for a median duration of 6.4 years. VE was also evaluated for phase B alone. All children's parents/guardians were provided with diary cards to record maximum information related to varicella/zoster case(s) to aid grading of severity.

Case ascertainment and confirmation have been described previously [14]. Briefly, the study followed a varicella case definition used by the Centers for Disease Control and Prevention (CDC) with slight modifications. A varicella case was confirmed when it met the clinical case definition and the polymerase chain reaction

(PCR) result was positive, or when it met the clinical definition, was confirmed by the IDMC and was epidemiologically linked to a valid index case.

The severity of varicella/zoster was assessed using the modified Vázquez scale [17]. These modifications were described previously [14].

To optimize the reporting procedures of suspected varicella/zoster cases and to ensure that the maximum number of cases were promptly identified and reported to the study sites, all children's parents/guardians were contacted by telephone between study visits (once every six months during phase B) to remind them to report to the investigator/study site any skin eruption that might be indicative of varicella/zoster their child may have.

2.3. Assessment of antibody persistence

A blood sample (4 mL) was collected from all children four and six years post-vaccination for determination of VZV antibodies and results were analyzed in comparison to antibody responses evaluated in phase A of the study (at Day 42, Day 84, Year 1 and Year 2).

The evaluation of antibody persistence at Year 6 was based on the adapted ATP cohort for persistence, i.e. excluding the serology results of children who did not respect the visit intervals for that specific phase. A child who did not respect the interval from Visit 3 to Year 2 but respected the interval from Visit 3 to Year 6 was excluded from the adapted cohort for Years 1 and 2 (phase A) but was included for Years 4 and 6 analyses (phase B). The data lock point for the Year 6 immunogenicity analysis was 17 December 2015.

Serum was analyzed by enzyme-linked immunosorbent assay (ELISA), with assay cut-off: 25 mIU/mL for antibodies against VZV, and dermal lesions and/or throat swabs were analyzed using PCR for all children.

A child seropositive for VZV had to have an antibody concentration greater than or equal to the cut-off value of 25 mIU/mL.

GMCs were calculated by taking the anti-log of the mean of the log concentrations for the assay. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC calculations. Additionally, all concentrations between 25 mIU/mL and 40 mIU/mL were given a value of 25 mIU/mL prior to log-transformation. Values below 25 mIU/mL were given an arbitrary value of 12.5 mIU/mL.

The identification and characterization of VZV DNA for qualitative (+/–) and strain identification (wild type/vaccine strain) was done using PCR-Restriction Fragment Length Polymorphism (RFLP) [18].

2.4. Safety assessment

The primary safety analyses were part of phase A. In phase B, only SAEs were recorded in the total vaccinated cohort (TVC), throughout the study (from 01 July 2009 until 17 December 2015). All complications of varicella/zoster cases (secondary bacterial infection of the skin, cerebellar ataxia, encephalitis, pneumonia, hepatitis, appendicitis, arthritis, glomerulonephritis, orchitis, pericarditis) were to be considered SAEs. The intensity and causality of each SAE was assessed and reported by the investigators.

2.5. Statistical analyses

Statistical analyses were previously described in detail [14]. The statistical analyses were descriptive and were done using SAS Drug Development version 3. The exact 95% CIs for a proportion within a group were calculated in SAS using the method of Clopper [19].

The VE computation was based on the hazard ratio (HR) estimated with the Cox proportional hazards regression model, which

takes into account the individual follow-up time of each child and censored data [20], using the formula $VE = 100 \times (1 - HR)$. Efficacy was assessed in the ATP cohort for efficacy, which included all children who completed their vaccinations and respected the protocol requirements.

The TVC included all children who received at least one dose of study vaccine during phase A.

3. Results

3.1. Study population

Of the 5803 children enrolled and vaccinated (TVC) in phase A, 4580 were included in the TVC in phase B, and 3829 (66%) completed the study up to Year 6; 5289 and 3791 were included in the ATP cohort for efficacy in phase A + B and phase B, respectively (Fig. 1).

The three treatment groups were well-balanced with regard to demographic characteristics and to the proportion of children with different levels of contact based on care type. The mean age at first vaccine dose and the other demographic characteristics for the ATP cohort for efficacy were similar in phase A + B and phase B (Table 1).

3.2. Vaccine efficacy

During the median 6.4 years of follow-up in phase A + B, the number (percentage) of children with a reported contact with varicella and/or zoster disease was 764 (33.5% [95% CI: 31.6–35.5]) in the MMRV group, 730 (32.2% [95% CI: 30.3–34.2]) in the MMR+V group and 211 (28.4% [95% CI: 25.1–31.7]) in the MMR control group. The VE of two doses of MMRV against all and against moderate or severe varicella was 95.0% (95% CI: 93.6–96.2) and 99.0% (95% CI: 97.7–99.6), respectively. Efficacy of one dose of varicella vaccine (MMR+V) against all and against moderate or severe varicella was 67.0% (95% CI: 61.8–71.4) and 90.3% (95% CI: 86.9–92.8), respectively. After a median follow-up of 3.3 years, similar efficacy was observed in phase B alone (Table 2).

No severe confirmed varicella was reported in the MMRV group (receiving 2 doses of varicella vaccine) and one case was reported in the MMR+V group (receiving 1 dose of varicella vaccine) as compared to six cases in the MMR control group (receiving no varicella vaccine). The majority of confirmed first varicella cases were mild in the MMRV and MMR+V groups (91.5% [95% CI: 82.5–96.8] and 87.1% [95% CI: 83.5–90.2], respectively); more than half of the cases in the MMR control group were moderately severe or severe (Table 3).

Among the children who developed a breakthrough case of varicella in the MMRV and MMR+V groups during the follow-up period, the majority (87.3% [95% CI: 77.3–94.0] and 76.6% [95% CI: 72.3–80.6], respectively) had ≤ 50 lesions. 33.8% [95% CI: 28.7–39.3] of those with confirmed varicella disease in the MMR control group exhibited 1–50 lesions and the majority had > 50 lesions (32.6% [95% CI: 27.5–38.0] with 51–100 lesions, 29.5% [95% CI: 24.6–34.8] with 101–500 lesions and 3.7% [95% CI: 1.9–6.4] with > 500 lesions). Within each group, similar distribution was observed by severity or by number of lesions in phase B compared to phase A + B (Table 3).

In phase A + B, the majority of first confirmed varicella cases that exhibited predominantly vesicular lesions ranged from 46.5% (95% CI: 34.5–58.7) in the MMRV group to 70.8% (95% CI: 65.5–75.7) (Table 3). In phase B, most first confirmed varicella cases exhibited predominantly papular lesions in the MMRV (45.0 [95% CI: 29.3–61.5]) and MMR+V (50.8 [95% CI: 43.4–58.2]) groups,

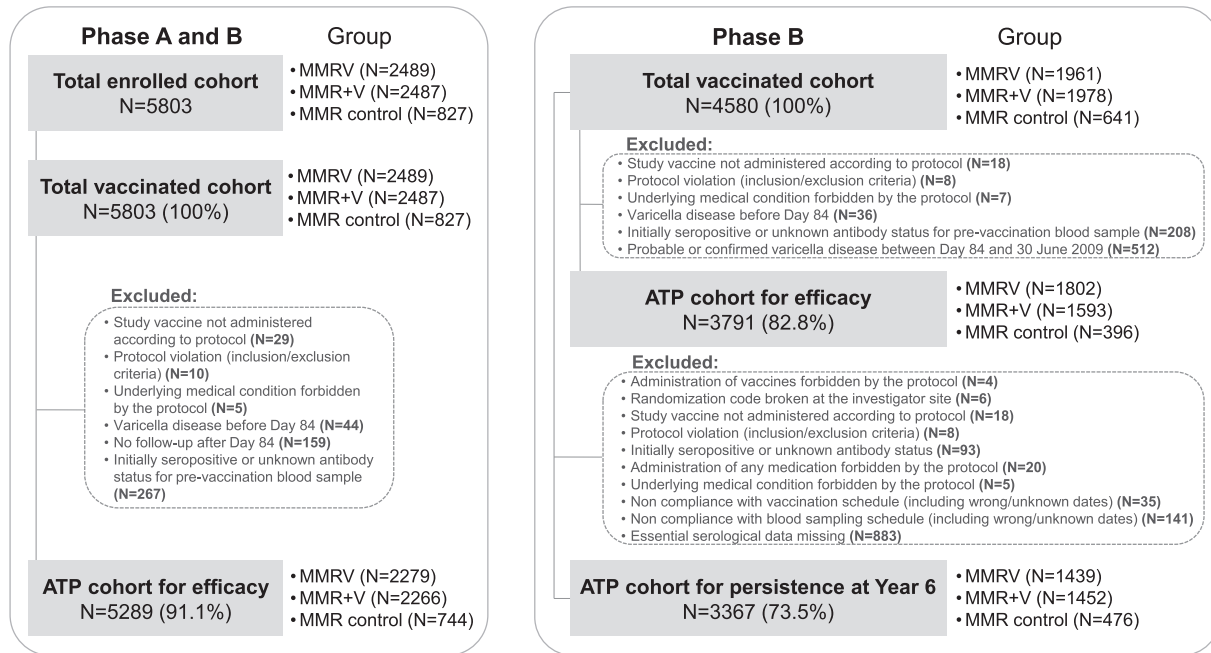


Fig. 1. Flow chart of children in the study with reasons for elimination from according-to-protocol analyses. N, number of children in each group/cohort; ATP, according-to-protocol; MMRV, children who received two doses of the combined measles-mumps-rubella-varicella vaccine (at Day 0 and Day 42); MMR+V, children who received one dose of MMR (at Day 0) and one dose of monovalent varicella vaccine (at Day 42); MMR, children who received two doses of the measles-mumps-rubella vaccine (active control, at Day 0 and Day 42).

Table 1
Demographic characteristics of the children in phase A + B and phase B of the study (ATP cohort for efficacy).

Characteristic	Phase A + B			Phase B		
	MMRV (N = 2279)	MMR+V (N = 2266)	Control (N = 744)	MMRV (N = 1802)	MMR+V (N = 1593)	Control (N = 396)
Mean age (months) at first vaccine dose ± SD	14.2 ± 2.5	14.2 ± 2.4	14.3 ± 2.5	14.3 ± 2.4	14.2 ± 2.5	14.1 ± 2.4
Gender						
Female, n (%)	1057 (46.4)	1109 (48.9)	360 (48.4)	826 (45.8)	793 (49.8)	186 (47.0)
Ethnicity						
White – Caucasian heritage, n (%)	2227 (97.7)	2227 (98.3)	737 (99.1)	1763 (97.8)	1573 (98.7)	393 (99.2)
Arabic/North African heritage, n (%)	21 (0.9)	7 (0.3)	2 (0.3)	14 (0.8)	2 (0.1)	1 (0.3)
Other, n (%)	31 (1.4)	32 (1.4)	5 (0.6)	25 (1.4)	18 (1.2)	2 (0.5)
Country						
Czech Republic, n (%)	525 (23.0)	516 (22.8)	171 (23.0)	507 (28.1)	412 (25.9)	82 (20.7)
Greece, n (%)	115 (5.0)	113 (5.0)	32 (4.3)	–	–	–
Italy, n (%)	106 (4.7)	109 (4.8)	35 (4.7)	89 (4.9)	82 (5.1)	16 (4.0)
Lithuania, n (%)	256 (11.2)	255 (11.3)	86 (11.6)	241 (13.4)	218 (13.7)	65 (16.4)
Norway, n (%)	74 (3.2)	76 (3.4)	25 (3.4)	65 (3.6)	57 (3.6)	10 (2.5)
Poland, n (%)	385 (16.9)	368 (16.2)	116 (15.6)	350 (19.4)	320 (20.1)	89 (22.5)
Romania, n (%)	121 (5.3)	126 (5.6)	42 (5.6)	81 (4.5)	75 (4.7)	24 (6.1)
Russia, n (%)	378 (16.6)	392 (17.3)	130 (17.5)	181 (10.0)	185 (11.6)	49 (12.4)
Slovakia, n (%)	199 (8.7)	195 (8.6)	68 (9.1)	191 (10.6)	173 (10.9)	46 (11.6)
Sweden, n (%)	120 (5.3)	116 (5.1)	39 (5.2)	97 (5.4)	71 (4.5)	15 (3.8)
Care type						
At least one sibling at home, n (%)	655 (28.7)	592 (26.1)	192 (25.8)	528 (29.3)	397 (24.9)	93 (23.5)
Attending day care center, n (%)	525 (23.0)	546 (24.1)	187 (25.1)	356 (19.8)	320 (20.1)	78 (19.7)
Attending a childminder, n (%)	148 (6.5)	155 (6.8)	57 (7.7)	106 (5.9)	94 (5.9)	25 (6.3)
At least once a week contact, ^a n (%)	2051 (90.0)	2055 (90.7)	680 (91.4)	1618 (89.8)	1449 (91.0)	363 (91.7)

ATP, according-to-protocol; N, total number of children in the respective phase; SD, standard deviation; n (%), number (percentage) of children in a given category; other, Black, East/South East Asian, American Hispanic, Japanese and other heritage.

Note: demographic characteristics for phase A have previously been presented.

^a With other children without a known positive history of varicella disease or vaccination.

while in the MMR group the majority of cases (51.2 [95% CI: 42.1–60.2]) exhibited vesicular lesions (Table 3).

The highest rates of confirmed varicella cases over time were recorded from October to June in the MMR group.

There were three confirmed HZ cases (one in MMR+V group and two in MMR group); all were mild and all children had a previous PCR-confirmed varicella case; all confirmed HZ cases tested positive for the wild-type virus. The interval between the onset of pri-

Table 2

Vaccine efficacy against all, moderate and severe, and severe confirmed varicella cases (A) from six weeks after dose 2, or (B) from the beginning of phase B until data lock point for the Year 6 analysis (ATP cohort for efficacy).

Disease severity	Study group	Phase A + B		Phase B	
		n/N	Vaccine efficacy (95% CI)	n/N	Vaccine efficacy (95% CI)
All varicella cases	MMRV	71/2279	95.0 (93.6–96.2)	33/1800	95.3 (93.1–96.8)
	MMR+V	419/2266	67.0 (61.8–71.4)	176/1592	69.5 (61.5–75.8)
Moderate or severe varicella cases	MMRV	6/2279	99.0 (97.7–99.6)	4/1800	98.4 (95.5–99.4)
	MMR+V	58/2266	90.3 (86.9–92.8)	18/1592	91.8 (85.9–95.2)
Severe varicella cases	MMRV	0/2279	100 (undefined)	0/1800	100 (undefined)
	MMR+V	1/2266	94.6 (55.3–99.4)	0/1592	100 (undefined)

Confirmed varicella case, a case that met the clinical case definition and the PCR result was positive, or met the clinical definition, was confirmed by the Independent Data Monitoring Committee and was epidemiologically linked to a valid index case [14]; ATP, according-to-protocol; MMRV, children who received two doses of the combined measles-mumps-rubella-varicella vaccine (at Day 0 and Day 42); MMR+V, children who received one dose of MMR (at Day 0) and one dose of monovalent varicella vaccine (at Day 42); N, number of children included in each group (without missing values); n, number of children reporting at least one event in each group; CI, confidence interval.

Table 3

Disease severity and number of lesions for the first confirmed varicella cases (ATP cohort for efficacy).

	Phase A + B			Phase B		
	Percentage of all cases (95% CI)			Percentage of all cases (95% CI)		
	MMRV N = 71	MMR+V N = 419	MMR N = 325	MMRV N = 40	MMR+V N = 185	MMR N = 125
Severity	<i>According to disease severity</i>					
Mild	91.5 (82.5–96.8)	87.1 (83.5–90.2)	48.9 (43.4–54.5)	90.0 (76.3–97.2)	90.3 (85.1–94.1)	59.2 (50.1–67.9)
Moderately severe	8.5 (3.2–17.5)	12.9 (9.8–16.5)	49.2 (43.7–54.8)	10.0 (2.8–23.7)	9.7 (5.9–14.9)	37.6 (29.1–46.7)
Severe	0.0 (0.0–5.1)	0.0 (0.0–0.9)	1.8 (0.7–4.0)	0.0 (0.0–8.8)	0.0 (0.0–2.0)	3.2 (0.9–8.0)
Number of lesions	<i>According to number of lesions</i>					
1–50	87.3 (77.3–94.0)	76.6 (72.3–80.6)	33.8 (28.7–39.3)	80.0 (64.4–90.9)	79.5 (72.9–85.0)	48.8 (39.8–57.9)
51–100	11.3 (5.0–21.0)	16.7 (13.3–20.6)	32.6 (27.5–38.0)	17.5 (7.3–32.8)	14.1 (9.4–19.9)	26.4 (18.9–35.0)
101–500	1.4 (0.0–7.6)	5.7 (3.7–8.4)	29.5 (24.6–34.8)	2.5 (0.1–13.2)	5.4 (2.6–9.7)	20.0 (13.4–28.1)
≥501	0.0 (0.0–5.1)	0.2 (0.0–1.3)	3.7 (1.9–6.4)	0.0 (0.0–8.8)	0.0 (0.0–2.0)	4.8 (1.8–10.2)
Predominant type of lesions	<i>According to predominant type of lesions</i>					
Macular	8.5 (3.2–17.5)	2.1 (1.0–4.0)	0.0 (0.0–1.1)	10.0 (2.8–23.7)	3.2 (1.2–6.9)	0.8 (0.0–4.4)
Papular	42.3 (30.6–54.6)	45.1 (40.3–50.0)	26.5 (21.7–31.6)	45.0 (29.3–61.5)	50.8 (43.4–58.2)	45.6 (36.7–54.7)
Vesicular	46.5 (34.5–58.7)	51.1 (46.2–56.0)	70.8 (65.5–75.7)	40.0 (24.9–56.7)	42.2 (35.0–49.6)	51.2 (42.1–60.2)
Hemorrhagic	2.8 (0.3–9.8)	1.0 (0.3–2.4)	2.5 (1.1–4.8)	5.0 (0.6–16.9)	2.2 (0.6–5.4)	2.4 (0.5–6.9)

ATP, according-to-protocol; MMRV, children who received two doses of the combined measles-mumps-rubella-varicella vaccine (at Day 0 and Day 42); MMR+V, children who received one dose of MMR (at Day 0) and one dose of monovalent varicella vaccine (at Day 42); MMR, children who received two doses of the measles-mumps-rubella vaccine (active control, at Day 0 and Day 42); N, number of children with varicella cases in each group. Disease severity was: mild disease (≤ 7 points); moderately severe disease (8–15 points); severe disease (≥ 16 points) scored by Independent Data Monitoring Committee using the modified Vázquez scale [17].

mary disease and the onset of HZ was between 15 and 57 months. Two cases (one in MMR+V and one in MMR group) had papular and one (MMR group) had vesicular lesions.

3.3. Antibody persistence

Two doses of MMRV and one dose of MMR+V induced antibody responses against VZV that persisted for up to 6 years after vaccination, with GMCs at least 5-fold greater than the seroconversion threshold at all time points assessed, with and without censoring of post-infection data. Compared to Year 2, anti-VZV concentrations also increased in the MMR group at Year 4 and Year 6, with a value 3.6-fold greater than the threshold being observed at Year 6 (Fig. 2). The percentage of seronegative children in the control group decreased from 97.8% (95% CI: 95.0–99.3) (at Day 42) to 44.9% (95% CI: 37.4–52.6) (at Year 6). By country (except Greece, where centers were closed prior to the start of Phase B due to implementation of varicella vaccination program), at year 6, the proportion of seronegative children varied from 0% (95% CI: 0–28.5) in Romania to 80% (95% CI: 28.4–99.5) in Sweden.

3.4. Safety

From the start of phase B to Year 6, a total of 570 SAEs were reported for 422 children; none of the SAEs were fatal or considered vaccine-related by the investigator.

Four children reported SAEs (leukemia, rhabdomyosarcoma, lymphadenopathy, and thrombocytopenia) that resulted in withdrawal from the study.

4. Discussion

This is, to our knowledge, the first study to assess the VE of one- or two-dose varicella vaccination, in the presence of a control group, over a period of approximately 6 years. Data on longer term protection (10 years) is currently being collected.

After a follow-up of 6 years (median: 6.4 years), the efficacy of two doses of MMRV against all varicella and against moderate to severe varicella was >95%. This protection was greater than that provided by one dose of MMR+V, which had an efficacy against all varicella of 67.0%, and against moderate to severe varicella of >90.0%. Compared to Year 3 data [14] it can be observed that protection against varicella was sustained for up to 6 years post-vaccination, as there was no diminution of VE. It is also notable that the vast majority of breakthrough varicella cases in the MMRV and MMR+V groups (87.3% and 76.6%, respectively) were mild (<50 lesions). In the control group varicella cases with <50 lesions occurred in only 33.8% of the children. The incidence of HZ in the control group is too low to comment on the impact of vaccination on this disease although it can be noted that there were no reported cases in the MMRV group.

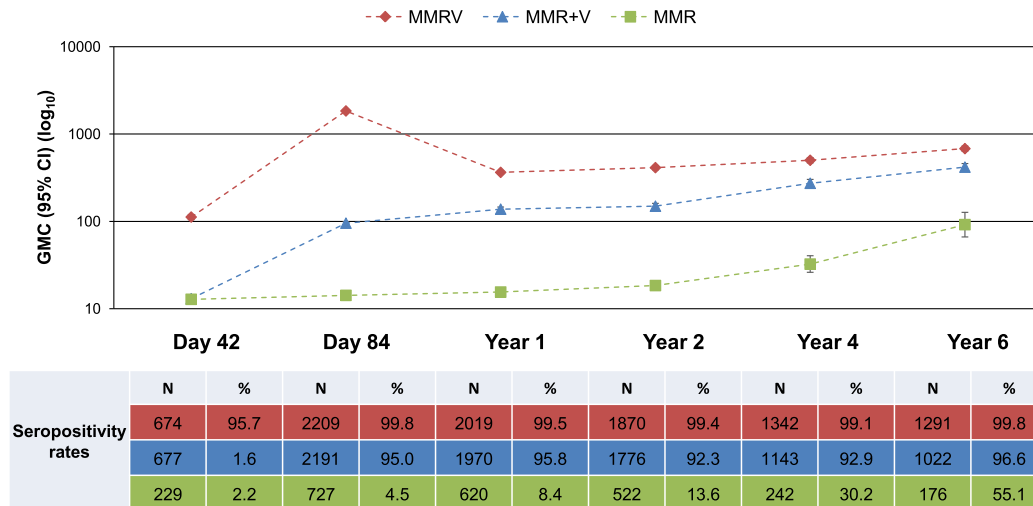


Fig. 2. Anti-VZV GMCs and seroresponse to varicella vaccination in initially seronegative children with post-infection data considered missing (adapted persistence cohort). GMC, geometric mean concentration; CI, confidence interval; VZV, varicella zoster virus; MMRV, children who received two doses of the combined measles-mumps-rubella-varicella vaccine (at Day 0 and Day 42); MMR+V, children who received one dose of MMR (at Day 0) and one dose of monovalent varicella vaccine (at Day 42); MMR, children who received two doses of the measles-mumps-rubella vaccine (active control, at Day 0 and Day 42); N, number of children with available results; %, percentage of children with anti-VZV concentration ≥ 25 mIU/mL. Error bars depict 95% CIs.

In the control group, at year 6, there were still 79 children (44.9%) seronegative for anti-VZV antibodies and these children remaining susceptible to VZV infection/disease. The increase in GMC overtime in the control group despite post-infection data being considered missing indicates that there is a degree of under-reporting of varicella cases or subjects are experiencing subclinical varicella infection. If this proportion is generalized to the entire remaining control group, an efficacy estimate at 10 years is expected to be informative.

From 3 to 6 years post-vaccination no safety concerns were identified, with none of the SAEs being assessed by the investigators as vaccine-related. These results support the vaccines' known clinically acceptable safety profiles [21].

The strengths of this trial, conferring it robustness, are its multinational and multiyear design, the inclusion of a control group, its rigorous case confirmation procedures, and the fact that it was not conducted in countries with UMV against varicella. The fact that active surveillance was done to identify varicella cases and that a blinded adjudication committee was used to assess suspected cases are also strong points. Some of its limitations include loss to follow-up over the cohort's periods, racial homogeneity of the children, not all cases being presented (and even when presented no systematic picture record) and unblinding of some children in the MMR+V group (could be biased if parents brought children with rash illness to medical attention).

Our data suggest that implementation of two-dose varicella vaccination in children during their second year of life ensures optimum protection against all forms of varicella disease.

5. Conclusions

The efficacy of two doses of MMRV and one dose of MMR+V persisted through >6 years post-vaccination, with two doses of MMRV being highly efficacious against varicella of any severity and one dose of MMR+V being highly efficacious against moderate/severe disease with moderate protection against milder disease. No safety issues were identified.

Trademark statement

Varilrix, *Priorix* and *Priorix-Tetra* are trademarks of the GSK group of companies.

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Author's contribution

OH and BI contributed to the conception, design and planning of the study. MP contributed as statistician to the method and selection development, the statistical data analysis, the reporting of data and the assessment of robustness of this manuscript. All authors contributed to the acquisition and review of the data. JB, HC, GL, OR, RG, PP, DP, MGD, RK and GG recruited patients. All authors contributed to the interpretation of data and the drafting of the report. They revised it critically for important intellectual content and approved the version to be published.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Ouzama Henry and Michael Povey are employed by the GSK group of companies. Bruce Innis was employed by the GSK group of companies at the time of the study and is now an employee of PATH. Bruce Innis and Ouzama Henry hold shares in the GSK group of companies as part of their employee remuneration. Giovanni Gabutti's previous institute (LHU4 "Chiavarese", Liguria Region) received payment for his participation as a principal investigator in the trial; he has received payment from the GSK group of companies, Sanofi Pasteur, MSD Italy and Sequirus for participation as a board

member, and received consulting and lecture fees from the GSK group of companies, Novartis, Sanofi Pasteur MSD, and Pfizer. Hanna Czajka received payment for her participation as a principal investigator in this trial. All other authors declare no potential conflict of interest.

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