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RESEARCH PAPER

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A randomized trial assessing the efficacy, immunogenicity, and safety of vaccination with live attenuated varicella zoster virus-containing vaccines: ten-year follow-up in Russian children

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ABSTRACT

In Russia, a universal varicella vaccination (UVV) program has not been implemented, and varicella vaccination coverage is low. We assessed the efficacy, antibody persistence, and safety of one- and two-dose varicella vaccination schedules in Russian children with a ten-year follow-up period, as part of an international phase IIIB, observer-blind, randomized, controlled trial (NCT00226499). Children aged 12–22 months were randomized (3:3:1) to receive two doses of tetravalent measles-mumps-rubella-varicella vaccine (V2 group), one dose trivalent measles-mumps-rubella (MMR) vaccine and one dose of varicella vaccine (V1 group), or two doses of MMR vaccine (V0 [control] group), 42 days apart. Main study outcomes were: vaccine efficacy (VE) against confirmed varicella cases, anti-varicella zoster virus (VZV) seropositivity rates and geometric mean concentrations, and reporting of (serious) adverse events ([S]AEs). The total vaccinated cohort in Russia comprised 1000 children; 900 were followed up until study end (year [Y] 10). VE estimates against confirmed varicella (Y10) were 92.4% in the V2 group and 74.7% in the V1 group. Anti-VZV seropositivity rates remained ≥99.4% in the V2 group and ≥89.7% in the V1 group from day 42 post-vaccination 2 until Y10. Occurrence of (un)solicited AEs and SAEs was similar across groups and confirmed the safety profile of the vaccines. No vaccination-related SAEs or deaths were reported. These results are consistent with the global trial results, i.e., the highest VE estimates observed following the two-dose schedule compared to the one-dose schedule. These data may inform decision-making related to potential implementation of a UVV program.

PLAIN LANGUAGE SUMMARY

What is the context?

- Varicella is a common childhood disease caused by the highly contagious varicella zoster virus.
- Varicella vaccines have been used for more than three decades.
- A large clinical trial conducted in ten countriesassessed the efficacy and safety of one dose of monovalent varicella vaccine or two doses of combined varicella vaccine (MMRV). The enrolled children were also followed up for a ten-year period to evaluate the persistence of the immune response and the long-termefficacy of the vaccine.

What is new?

- Here, we present the long-term efficacy, immunogenicity, and safety results in the cohort of children enrolled in Russia, as part of the global ten-year follow-up study.
- We found that:
  - The monovalent and combined vaccines reduced the number of varicella cases.
  - The MMRV two-dose regimen displayed higher efficacy in preventing varicella of all severities compared to the one-dose regimen.
  - The immune response conferred by the vaccine persisted up to ten years post-vaccination.
  - No vaccination-related deaths occurred, and no safety concerns were raised.

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Antibody persistence; children; long-term efficacy; Russia; combined vaccination; varicella

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What is the impact?

- Vaccination against varicella resulted in long-term protective efficacy and antibody persistence over ten years post-vaccination in Russian children.
- Although one-dose varicella vaccination was effective at protecting against varicella, a two-dose schedule provided a more complete protection. This could inform health policy decisions regarding the implementation of varicella vaccination in routine immunization program in Russia.

Introduction

Varicella zoster virus (VZV) causes varicella (chickenpox) disease, which is highly infectious and affects mostly children. After a first VZV infection, the virus persists in the host's body and may reactivate later in life to cause herpes zoster (HZ, shingles).[1] Although varicella is mostly mild in children, potentially severe complications, such as stroke, encephalitis, and secondary bacterial infections, may occur.[1–3] The global burden of varicella disease is high, with approximately 4.2 million complications requiring hospitalization and 4,200 associated deaths, annually.[1] It has been estimated that approximately 90% of children living in temperate climates become infected with VZV by the age of 15 years.[4,5] In Russia, more than 820,000 varicella cases were reported in 2019, representing an annual incidence of 559.1 cases per 100,000 population. More than 90% of these cases occurred in children, and approximately 70% in one- to six-year-olds.[6]

The currently available varicella vaccine formulations include monovalent varicella (V) vaccines, and tetravalent vaccines combining antigens against measles, mumps, rubella, and varicella (MMRV).[1] Two doses of either formulation have demonstrated >90% efficacy against varicella disease in randomized clinical trials.[7–9]

Universal varicella vaccination (UVV) with one dose of a monovalent V vaccine was first introduced in the routine childhood immunization program in the United States of America (USA) in 1995.[10,11] By 2004, vaccine uptake in the USA had reached approximately 90%, resulting in significant reductions in varicella incidence and associated hospitalization rates.[12–14] Similar UVV programs have been subsequently introduced by other countries in other regions of the world, resulting in significant reductions in the varicella disease burden.[15,16]

The use of a one-dose varicella vaccination schedule has been shown to be associated with vaccine efficacy (VE) estimates of ≥88% in randomized clinical trials.[8,17,18] However, this schedule was also associated with breakthrough disease,[19–21] with reported incidences ranging from 2.8% to 27.7%.[22–26] This observation prompted some countries to introduce a UVV program based on a two-dose schedule.[19,27] The World Health Organization (WHO) recommends that the dosing schedule should be determined depending on the programmatic goal: while one dose is adequate for reducing mortality and severe morbidity, two doses further limit disease outbreaks.[1] This WHO recommendation is supported by data showing that fewer disease outbreaks occur in countries that implemented a two-dose UVV program.[23,27,28]

In Russia, two monovalent V vaccines are licensed: Varilrix (GSK) and Varivax (Merck).[29,30] The Russian Ministry of Health has approved vaccination with Varilrix according to a two-dose schedule with the first dose administered at the age of 12 months, and the second dose at least six weeks later.[29,31] The Union of Pediatricians of Russia recommends the second dose being administered at 6 years of age to allow use of the tetravalent MMRV vaccine in the Russian national calendar of preventive vaccinations and thereby decrease the number of vaccination visits needed throughout childhood.[32] While varicella vaccination is included in certain regional immunization programs, to date, there is no UVV program at the country level.[31,33] The regional immunization programs may apply universal vaccination, or target immunocompromised patients and/or social and professional risk groups, such as children attending a day care center or military recruits who were not previously vaccinated.[31] Regions where a varicella vaccination program is implemented reported a 75% lower varicella incidence than the national average in 2017.[34] Nevertheless, vaccination coverage remains low; in 2018, only approximately 5% of children aged 3 to 6 years were vaccinated against varicella.[32,35]

To further assess varicella vaccination in Europe, we conducted a phase IIIB, randomized, controlled trial in 10 European countries to evaluate the long-term efficacy, immunogenicity, and safety of varicella vaccination.[7,9,36] The tetravalent MMRV vaccine was administered as a two-dose schedule, while the monovalent V vaccine was administered as one dose following one dose of the trivalent measles, mumps, and rubella (MMR) vaccine.

The global results of the study have been published.[7,9,36,37] After 10 years of follow-up, VE against all varicella was 95.4% in children who received two doses of tetravalent MMRV vaccine and 67.2% in children who received one dose of monovalent V vaccine. VE against moderate to severe varicella was 99.1% and 89.5% for the two-dose VZV-containing vaccine (VCV) and one-dose VCV group, respectively.[9] Similar VE estimates were observed after 3 and 6 years of follow-up.[7,36] Seropositivity rates across groups receiving a VCV remained high during the study and were ≥98% for the varicella antigen and ≥90% for MMR antigens after 10 years of follow-up.[9,37] Additionally, both vaccination schedules showed acceptable reactogenicity and safety profiles.[9] Here, we report the long-term efficacy, immunogenicity, and safety of one-dose or two-dose varicella immunization in the cohort of children enrolled in Russia. These data may inform the Russian authorities during decision-making related to potential implementation of a nationwide UVV program.[31,38–40]

A summary contextualizing the outcomes presented here is displayed in the Plain Language Summary (Figure 1) for the convenience of health-care professionals.

Plain Language Summary

What is the context?

- Varicella is a common childhood disease caused by the highly contagious varicella zoster virus.
- Varicella vaccines have been used for more than three decades.
- A large clinical trial conducted in ten countries assessed the efficacy and safety of one dose of monovalent varicella vaccine or two doses of combined varicella vaccine (MMRV). The enrolled children were also followed up for a ten-year period to evaluate the persistence of the immune response and the long-term efficacy of the vaccine.

What is new?

- Here, we present the long-term efficacy, immunogenicity, and safety results in the cohort of children enrolled in Russia, as part of the global ten-year follow-up study.
- We found that:
  - ✓ The monovalent and combined vaccines reduced the number of varicella cases.
  - ✓ The MMRV two-dose regimen displayed higher efficacy in preventing varicella of all severities compared to the one-dose regimen.
  - ✓ The immune response conferred by the vaccine persisted up to ten years post-vaccination.
  - ✓ No vaccination-related deaths occurred, and no safety concerns were raised.

What is the impact?

- Vaccination against varicella resulted in long-term protective efficacy and antibody persistence over ten years post-vaccination in Russian children.
- Although one-dose varicella vaccination was effective at protecting against varicella, a two-dose schedule provided a more complete protection. This could inform health policy decisions regarding the implementation of varicella vaccination in routine immunization program in Russia.

Figure 1. Plain language summary to summarize the findings and highlight their clinical relevance.

Participants and methods

Study design

This study was a phase IIIB, observer-blind, randomized, controlled trial conducted between September 2005 and December 2016 in Czech Republic, Greece, Italy, Lithuania, Norway, Poland, Romania, Russia, Slovakia, and Sweden. Children were enrolled and randomly assigned (3:3:1) to receive two doses of tetravalent MMRV vaccine (Priorix-Tetra, GSK; V2 group), one dose of trivalent MMR vaccine (Priorix, GSK) followed by one dose of monovalent V vaccine (Varilrix, GSK; V1 group), or two doses of the MMR vaccine (V0 [control] group), 42 days apart. Here, we present results for Russia, generated in the context of this global study.

The trial consisted of two periods: phase A, which started on the day of first vaccination and lasted until year two; and phase B, which started from year two and lasted until study end (year 10). The phase A + B combined period for efficacy surveillance started 42 days post-vaccination two and extended until study end (year 10) (Figure 2). At the start of phase B, the study was

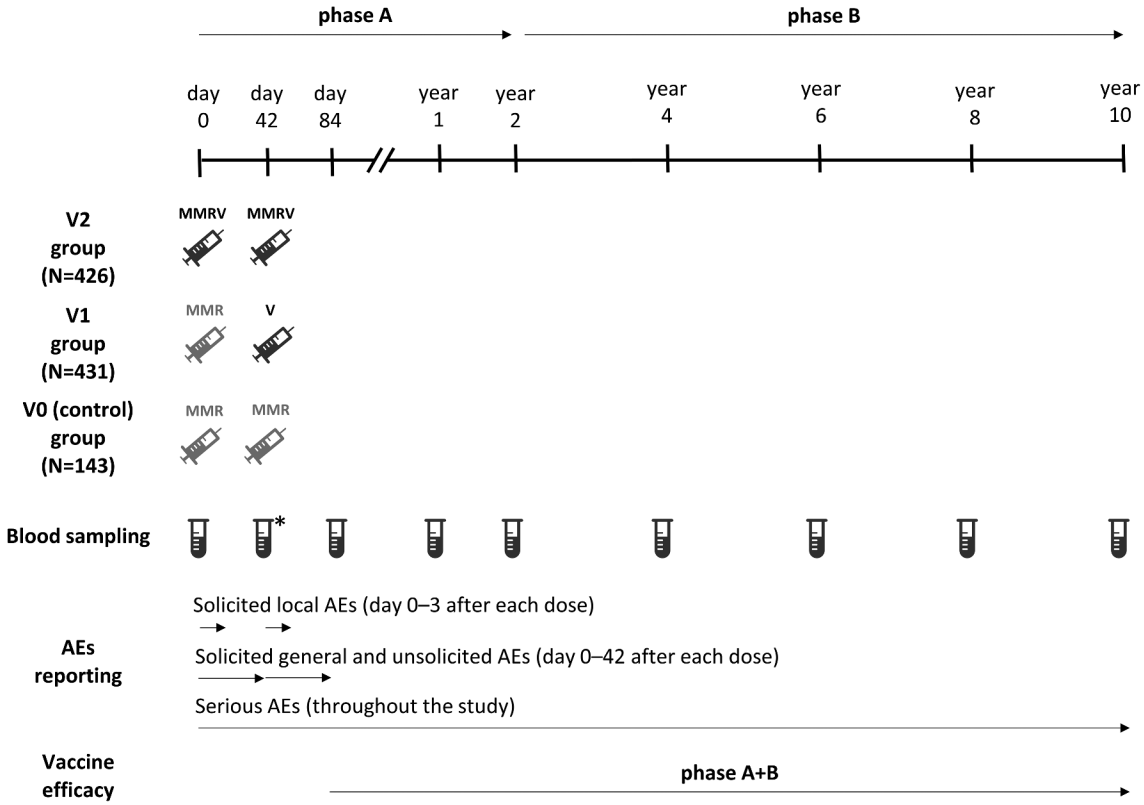


Figure 2. Study design. N, number of participants; AEs, adverse events; MMR, combined trivalent measles, mumps, and rubella vaccine; MMRV, combined tetravalent measles, mumps, rubella, and varicella vaccine; V, monovalent varicella vaccine; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of the tetravalent measles, mumps, rubella, and varicella vaccine.* only applicable to the subset for MMR testing.

discontinued in regions where varicella vaccination was introduced in the regional immunization program.

The study protocol, protocol amendments, and other study-related documents were reviewed and approved by the national, regional, or investigational center Independent Ethics Committee. The study is registered on ClinicalTrials.gov (NCT00226499) and was conducted in accordance with Good Clinical Practice principles, all applicable regulatory requirements, and the Declaration of Helsinki. All children's parents or legally acceptable representatives (LARs) provided written informed consent prior to the study procedures.

Participants

Participants were healthy children 12–22 months of age who had at least one sibling who was living at the same place and had no history of varicella disease/vaccination, were attending a day care center or a childminder with at least one child who had no known history of varicella disease/vaccination, or played at least once a week in close physical contact for at least 5 min with a child who had no known history of varicella disease/vaccination. Detailed eligibility criteria were previously published.[36,37]

Randomization and masking

Randomization has been described previously.[36] Administration of the vaccines and efficacy surveillance up to at least two years post-vaccination 2 was conducted in an observer-blind manner. In phase B, Russian children and their parents/LARs in the V1 group were unblinded because the country-recommended national immunization schedule includes a second dose of trivalent MMR vaccine at 6 years of age.[33]

Study vaccines

Three different lots of the tetravalent MMRV and monovalent V vaccines, and one lot of trivalent MMR vaccine were used. Both VCVs used in this study contain the live attenuated Oka strain.[41,42] The detailed composition of the study vaccines was published previously.[36] Vaccines were administered subcutaneously in the left deltoid region.

Efficacy assessment

All outcomes reported in the current analysis were secondary and descriptive. The efficacy objectives were to estimate efficacy of one dose of monovalent V (V1 group) or two doses of tetravalent MMRV vaccine (V2 group) in preventing confirmed varicella cases, and to assess the occurrence of complicated varicella cases from vaccination 1 until study end (phase A + B), in all groups.

Assessment of varicella cases is detailed in a previous publication.[36] The presence of VZV in samples collected from skin lesions was confirmed by restriction fragment length

polymorphism analysis following polymerase chain reaction (PCR) amplification. All cases of varicella-like rash were reviewed in a blinded manner by the independent data monitoring committee (IDMC). Based on the case description, PCR data, photographs of the lesion, and information regarding the child's contact with an active disease, the IDMC classified each suspected case as: no case, a confirmed varicella case (defined in the previous publication[36]), or a probable case. For the latter, the IDMC considered the case in agreement with the Centers for Disease Control and Prevention's clinical case definition (detailed in **supplementary methods**), but the case was not PCR-confirmed or epidemiologically linked to a varicella case that was identified as the source of infection.

Immunogenicity assessment

Anti-VZV immune responses were assessed in all children, and immune responses to measles, mumps, and rubella viruses were assessed in a subset of 200 children (subset for MMR testing) from six weeks post-vaccination 2 until year 2.

Blood samples for immunogenicity assessment were obtained from all children prior to administration of the first vaccine (pre-vaccination 1), at 84 days post-vaccination 1, and at years 1, 2, 4, 6, 8, and 10 of the study. An additional sample was obtained from children in the subset for MMR testing at 42 days post-vaccination 1. Anti-VZV (until year 10) and anti-measles, -mumps, and -rubella (until year 2) immunoglobulin G (IgG) antibody levels in serum were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Enzygnost, DiaSorin [formerly Siemens]).

Safety assessment

Serious adverse events (SAEs) were assessed in all children, and solicited local and general adverse events (AEs) and unsolicited AEs were assessed in the subset for MMR testing.

Solicited local AEs were recorded from day 0 to day 3, and solicited general and unsolicited AEs from day 0 to day 42, after each dose. SAEs were reported throughout the study. Solicited general AEs were fever, swelling of the salivary glands, meningism (including febrile seizures), and rash. Solicited AEs were graded 1–3 according to their intensity (grade 1–4 for rash as published previously[43]). The definition of grade 3 and medical events that were considered as SAEs are available in **supplementary methods**. Severity and causal association of all AEs with study vaccinations were assessed according to the investigator's clinical judgment.

Statistical analyses

Calculation of the sample size for the primary objectives of the global study was described previously.[36] All statistical analyses described here were descriptive. Statistical analyses were performed using the Statistical Analysis System (SAS) version 9.3 (including Proc-StatXact, version 8.1 module).

VE was calculated in the according-to-protocol (ATP) cohort for efficacy which included all children who completed vaccination and fulfilled protocol requirements. For VE calculations, data of children were censored at a varicella event, at the latest date with available data, at study end, or at the date at which mass vaccination with a VCV was implemented. The total time to event was calculated as the sum of the follow-up period expressed in years and censored at first occurrence of an event in each group. The incidence rate per 100 person-years was calculated as the number of children reporting at least one event in each group divided by the total time to event and was reported with its 95% confidence interval (CI). The Cox proportional hazards regression model without adjustments[44] was used to estimate the hazard ratio (HR) of experiencing a varicella event in the vaccinated group (V2 or V1 group) compared to the control group (V0 group). VE was estimated as 100×(1-HR) and was reported with its 95% CI, calculated in the same regression analysis. To assess robustness of the VE estimate for confirmed varicella cases, a post-hoc sensitivity analysis was done by performing the same calculations for the confirmed and probable varicella cases combined.

VZV immunogenicity outcomes were assessed in the adapted ATP cohort for persistence, which included children who completed vaccination, fulfilled protocol requirements, and complied with all visit intervals up to and including the timepoint considered. Anti-VZV antibody geometric mean concentrations (GMCs) were calculated by taking the anti-log of the mean of the log concentration transformation of all values equal to or above the limit of quantification (40 milli-international units [mIU]/mL) in children who were seronegative (i.e., children who had anti-VZV antibody levels below the assay cutoff [25 mIU/mL]) prior to vaccination. Before log-transformation, values below the cutoff were given an arbitrary value of half the cutoff. Values between 25 mIU/mL and 40 mIU/mL were given the value of 25 mIU/mL. All GMCs were reported with 95% CIs. Seropositivity rates were calculated at each timepoint as the percentage of children with anti-VZV antibody concentrations ≥25 mIU/mL and were reported with 95% CIs.

The levels of anti-measles, -mumps, and -rubella antibodies were measured up to two years post-vaccination 2 in the adapted ATP cohort for persistence in the subset for MMR testing; antibody GMCs were calculated by taking the anti-log of the mean of the log concentration transformation, in children who were seronegative prior to vaccination. Values below the cutoff (150 mIU/mL for anti-measles, 231 U/mL for anti-mumps, and 4 IU/mL for anti-rubella) were given the arbitrary value of half the cutoff. All GMCs were reported with 95% CIs. Seropositivity rates were calculated at each timepoint as the percentage of children with antibody concentrations equal or above the seropositivity thresholds (i.e., the assay cutoff in this study), and were reported with 95% CIs.

SAEs were assessed in the total vaccinated cohort (TVC), which included all children who received at least one dose of a study vaccine. AEs were assessed in the TVC in the subset for MMR testing. All safety endpoints were reported as number and proportion of children who reported the event, with 95% CIs.

Results

Study participants

A total of 5,803 children were enrolled in the global study between September 2005 and May 2006; in Russia, enrollment ended in February 2006. Among all children enrolled, 1,000

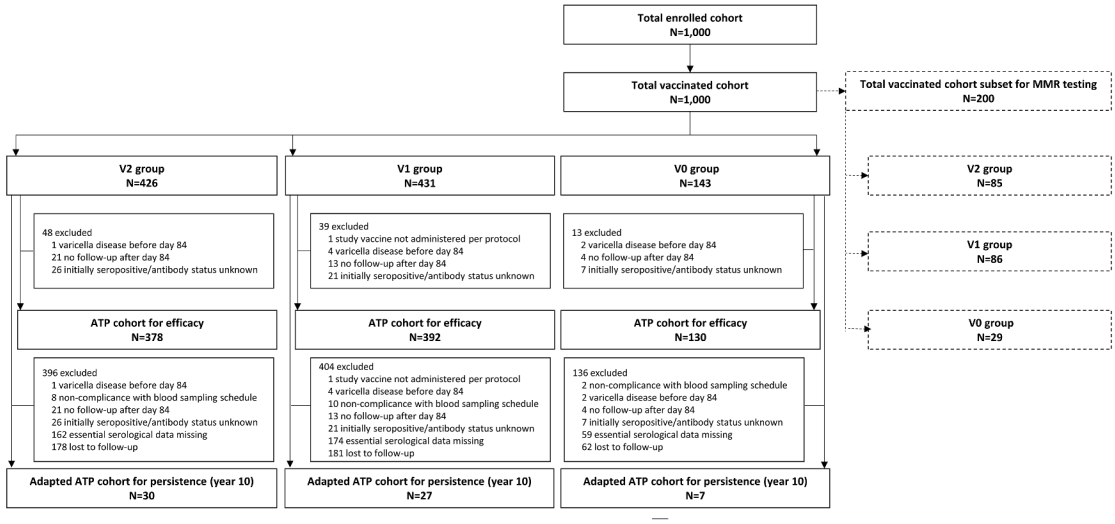


Figure 3. Participant flow chart. ATP, according-to-protocol; N, number of participants; MMR, measles, mumps, and rubella; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of the tetravalent measles, mumps, rubella, and varicella vaccine.

Table 1. Demographic characteristics of the study participants (total vaccinated cohort).

	V2 group N = 426	V1 group N = 431	V0 group* N = 143
Age in months, mean (± SD)	12.7 (1.7)	12.6 (1.4)	12.6 (1.2)
Female sex, n (%)	198 (46.5)	210 (48.7)	69 (48.3)
Race, n (%)			
White/Caucasian	423 (99.3)	428 (99.3)	143 (100)
Arabic/North African	1 (0.2)	0 (0.0)	0 (0.0)
East/South East Asian	2 (0.5)	2 (0.5)	0 (0.0)
South Asian	0 (0.0)	1 (0.2)	0 (0.0)
Contact with other children, n (%)			
At least one sibling at home	94 (22.1)	98 (22.7)	32 (22.4)
Attending a day care center	368 (86.4)	376 (87.2)	125 (87.4)
Attending a childminder	22 (5.2)	23 (5.3)	12 (8.4)
At least once a week at other places	392 (92.0)	399 (92.6)	131 (91.6)

N, total number of participants; n (%), number (percentage) of participants in a given category; SD, standard deviation; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of tetravalent measles, mumps, rubella, and varicella vaccine.
* data for the V0 group (control group) were also published in Gillard 2021.[45]

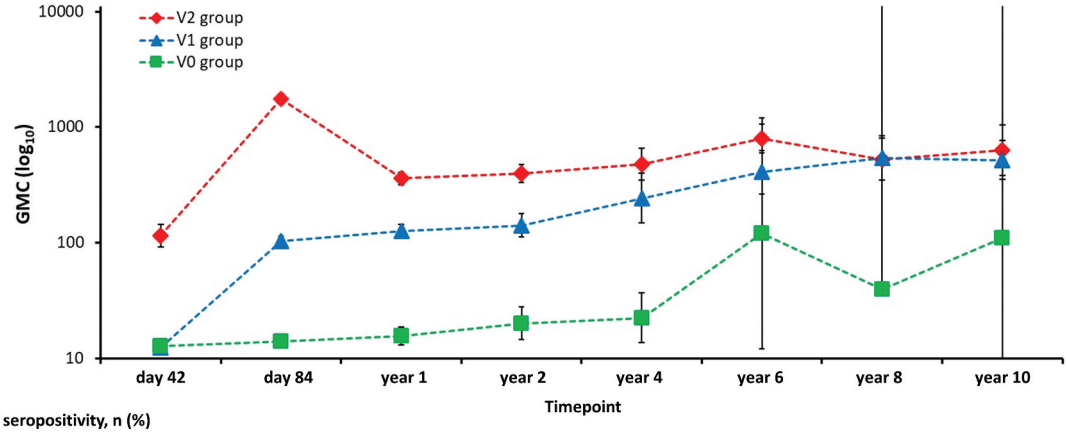
Table 2. Vaccine efficacy estimates against confirmed varicella cases (according-to-protocol cohort for efficacy).

	n/N	Total time to event (years)	Incidence rate (95% CI) per 100 person-years	Vaccine efficacy (95% CI)
V2 group	7/378	1480	0.5 (0.2–1.0)	92.4% (82.3–96.7)
V1 group	24/392	1471	1.6 (1.1–2.4)	74.7% (55.5–85.6)
V0 group	25/130	377	6.6* (4.5–9.8)	–

N, total number of participants; n, number of participants reporting at least one event; CI, confidence interval; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of tetravalent measles, mumps, rubella, and varicella vaccine.
* data for the V0 group (control group) were also published in Gillard 2021.[45]

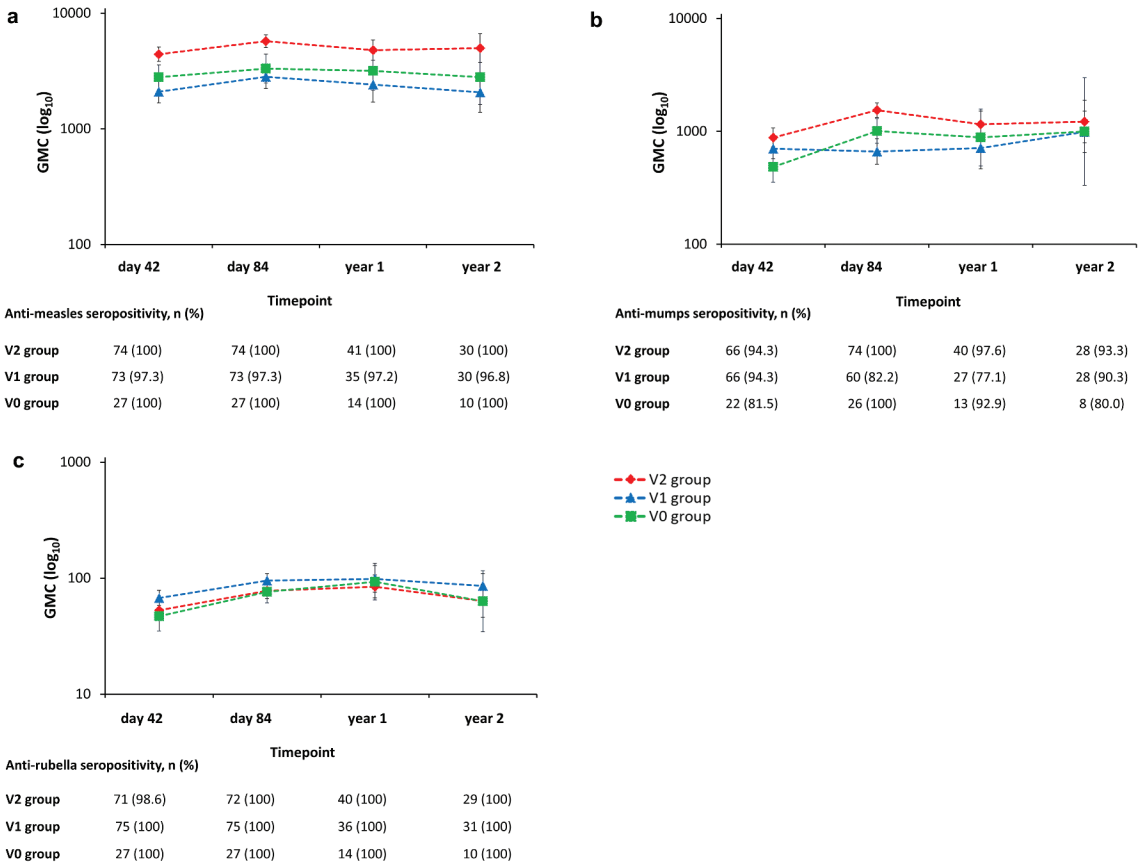
were included in the Russian TVC, of whom 426 were assigned to the V2 group, 431 to the V1 group, and 143 to the V0 group; 100 children were excluded from the ATP cohort for efficacy (Figure 3). Sixty-four children in the adapted ATP cohort for persistence completed the ten-year follow-up. The first 200 children enrolled in two pre-specified centers were included in the subset for MMR testing, of whom 85 were assigned to the V2 group, 86 to the V1 group, and 29 to the V0 group.

Demographic characteristics were balanced across the three groups (Table 1): the mean age at enrollment was 12.7 months and 47.7% of children were female. Most children (99.4%) were of Caucasian heritage.



Anti-VZV seropositivity, n (%)								
V2 group	70 (97.2)	358 (99.4)	267 (99.6)	186 (99.5)	48 (100)	50 (100)	26 (100)	27 (100)
V1 group	0 (0.0)	356 (96.0)	251 (95.4)	175 (89.7)	48 (90.6)	45 (97.8)	21 (100)	22 (100)
V0 group	1 (3.8)	6 (4.8)	8 (10.0)	11 (18.6)	5 (41.7)	5 (71.4)	1 (50.0)	2 (66.7)

Figure 4. Anti-varicella zoster virus (VZV) antibody persistence during ten years of follow-up (adapted according-to-protocol cohort for persistence). GMC, geometric mean concentration; n (%), number (percentage) of participants with anti-varicella zoster virus antibody geometric mean concentration equal to or above the limit of detection (25 mIU/mL); V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of the tetravalent measles, mumps, rubella, and varicella vaccine. The error bars represent the 95% confidence interval.



Anti-measles seropositivity, n (%)				
V2 group	74 (100)	74 (100)	41 (100)	30 (100)
V1 group	73 (97.3)	73 (97.3)	35 (97.2)	30 (96.8)
V0 group	27 (100)	27 (100)	14 (100)	10 (100)

Anti-mumps seropositivity, n (%)				
V2 group	66 (94.3)	74 (100)	40 (97.6)	28 (93.3)
V1 group	66 (94.3)	60 (82.2)	27 (77.1)	28 (90.3)
V0 group	22 (81.5)	26 (100)	13 (92.9)	8 (80.0)

Anti-rubella seropositivity, n (%)				
V2 group	71 (98.6)	72 (100)	40 (100)	29 (100)
V1 group	75 (100)	75 (100)	36 (100)	31 (100)
V0 group	27 (100)	27 (100)	14 (100)	10 (100)

Figure 5. Anti-measles (A), -mumps (B), and -rubella (C) antibody persistence during two years of follow-up (adapted according-to-protocol cohort for persistence, subset for MMR testing). GMC, geometric mean concentration; n (%), number (percentage) of participants with antibody GMC equal to or above the seropositivity threshold (150 mIU/mL for anti-measles, 231 U/mL for anti-mumps, and 4 IU/mL for anti-rubella antibodies); MMR, measles, mumps, and rubella; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of the tetravalent measles, mumps, rubella, and varicella vaccine. The error bars represent the 95% confidence interval.

Efficacy

The estimated VE against confirmed varicella cases was 92.4% in the V2 group and 74.7% in the V1 group (Table 2). A total of 56 varicella cases were confirmed across all groups during the 10 years of follow-up; the percentage of cases was lowest in the V2 group (1.9% [n = 7]), followed by V1 group (6.1% [n = 24])

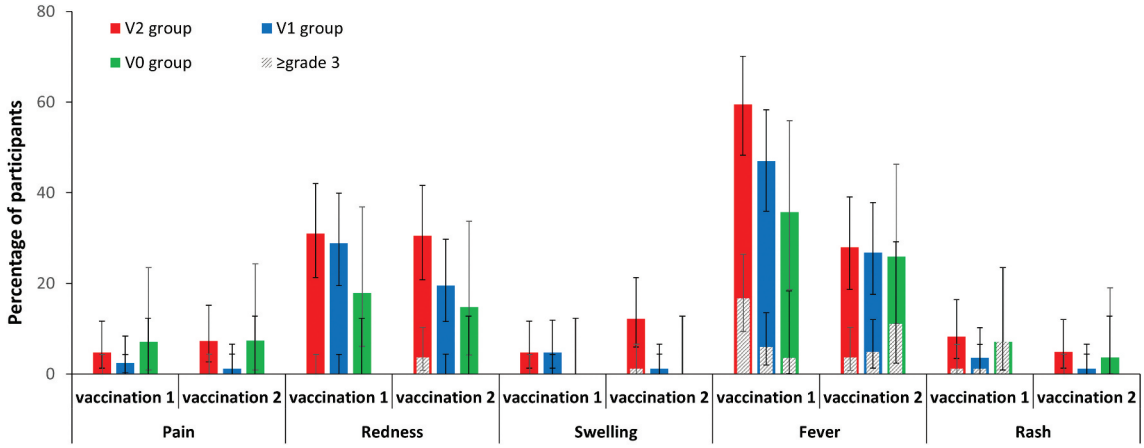


Figure 6. Incidence of solicited local adverse events (pain, redness, and swelling) from day 0 to day 3, and solicited general symptoms (fever and rash) from day 0 to day 42, after each dose (total vaccinated cohort, subset for MMR testing). MMR, measles, mumps, and rubella; V0 group, control group receiving two doses of trivalent measles, mumps, and rubella vaccine (no varicella vaccine); V1 group, group receiving one dose of trivalent measles, mumps, and rubella vaccine followed by one dose of monovalent varicella vaccine; V2 group, group receiving two doses of the tetravalent measles, mumps, rubella, and varicella vaccine. The error bars represent the 95% confidence interval. See **supplementary methods** for definition of grade 3 intensity.

and V0 group (19.2% [n = 25]) (Table 2). Robustness of these data was confirmed by the sensitivity analysis, which included probable varicella cases in addition to confirmed cases.

Immunogenicity

Forty-two days post-vaccination 2 (i.e., day 84 of the study), anti-VZV antibody seropositivity rates were 99.4% in the V2 group and 96.0% in the V1 group (Figure 4). Anti-VZV antibody seropositivity rates remained high in both groups (≥99.4% in the V2 group and ≥89.7% in the V1 group) from day 42 post-vaccination 2 until year 10. The evolution of GMCs over time paralleled that of seropositivity rates for both groups (Figure 4).

Anti-measles, -mumps, and -rubella antibody seropositivity rates were high in the V2 group (100%, ≥93.3%, and 100%, respectively) and in the V1 group (≥96.8%, ≥77.1%, and 100%, respectively) from day 42 post-vaccination 2 until year 2 (i.e., last sampling for this outcome) (Figure 5). Throughout the two-year follow-up period, GMCs for anti-measles, -mumps, and -rubella antibodies remained in similar ranges in the V2 group and the V1 group (Figure 5).

Safety

The most frequently reported solicited local AE was redness, reported by 31.0% of children in the V2 group, 28.9% in the V1 group, and 17.9% in the V0 group post-vaccination 1; and by 30.5%, 19.5%, and 14.8%, respectively, post-vaccination 2 (Figure 6). Fever occurred most frequently after vaccination 1 (in 35.7%–59.5% of children across groups). Grade 3 fever was reported by 3.6%–16.7% of children across groups. The incidence of other grade 3 AEs was limited. Non-varicella-like rash was reported by 3.6%–8.3% of children post-vaccination 1 and by 1.2%–4.9% of participants post-vaccination 2 across groups. Post-vaccination 1, all cases of rash reported by children in the V0 group were categorized as grade ≥3 (Figure 6). No cases of salivary gland swelling or meningism (including febrile seizures) were reported during the 43 days after each dose.

Unsolicited AEs were reported by 27.9%–35.3% of children post-vaccination 1 and by 17.9%–19.3% of children post-vaccination 2 across groups. The most frequently reported unsolicited AEs were: upper respiratory tract infection (n = 20), rhinitis (n = 12), and nasopharyngitis (n = 10) post-vaccination 1; and upper respiratory tract infection (n = 15), viral upper respiratory tract infection (n = 9), and rhinitis (n = 8) post-vaccination 2. Only one grade 3 unsolicited AE was reported, namely an upper respiratory tract infection in the V2 group post-vaccination 1.

A total of 184 SAEs were reported by 137 children throughout the study, among which two deaths occurred: one was caused by asphyxia during a fire and the other was an accidental death at home. None of these SAEs were considered causally related to vaccination. No HZ cases or complicated varicella cases were reported throughout the study.

Discussion

In this trial, we assessed the efficacy, immunogenicity, and safety of two vaccines containing the same live attenuated varicella Oka strain: the monovalent V vaccine, and the tetravalent MMRV vaccine. Vaccination of children according to a one-dose (V1 group) or two-dose (V2 group) VCV schedule allowed to estimate the efficacy of the two varicella vaccination schedules that can be considered for national immunization programs. Importantly, we used an accelerated vaccination schedule with a short interval (i.e., 42 days) between the two vaccinations. Such a shorter interval may improve adherence to complete and timely vaccination.[46] Furthermore, the risk of breakthrough varicella disease increases with time between two doses; hence, an accelerated schedule can help ensure that children are fully protected against varicella earlier in life.[47] However, a five-year interval between both doses may reduce the number of vaccination visits required, by allowing coadministration of the second dose with the tetanus and diphtheria vaccine at approximately 6 years of age.[33,38]

The long-term results obtained for children enrolled from Russia presented here may inform Russian authorities regarding

the potential implementation of a UVV program at the country level.[31,38–40] The results are generally in line with the previously published long-term global study results.[9] Our results suggest that the two-dose schedule provided optimal long-term efficacy, as shown by a lower number of breakthrough varicella cases and a higher VE estimate, compared to the one-dose schedule. A superior protection provided by two doses compared to one dose of any VCV was also demonstrated in a meta-analysis which included articles reporting effectiveness of both schedules. A two-dose schedule was shown to additionally reduce varicella disease by 79% (based on three randomized controlled trials), 63% (based on seven cohort studies), and 81% (based on five case-control studies) compared to a one-dose schedule.[21] Over the ten-year follow-up period, we observed more than three times more breakthrough varicella cases in children who received one dose VCV compared to children who received two doses of a VCV. Evidence from the global study demonstrated that most one-dose breakthrough cases (n = 469) were of mild or moderate nature except for one case, which was severe (<1%) (Russia-specific data is not available).[9] VE estimates against confirmed varicella cases were 74.7% with one dose and 92.4% with two doses of VCV. These estimates are in line with the 67.2% and 95.4% VE estimates, respectively, reported for the global study.[9] Additionally, these data are comparable to data from a systematic literature review and meta-analysis of dose-specific, post-licensure vaccine effectiveness estimates in healthy children (81% following one dose and 92% following two doses of any VCV).[28]

In a previously published meta-analysis which included 14 studies reporting outbreaks after one dose of a VCV, an overall VE of 72.5% was calculated.[48] Furthermore, that meta-analysis demonstrated waning of immunity over time post-vaccination. However, in the Russian cohort of the current trial, anti-VZV immune responses persisted in the two-dose and one-dose groups, with all children across both groups being seropositive at year 10. Part of these observed immune responses could be due to the study taking place in a country where varicella is endemic. Immunogenicity was assessed by measuring anti-VZV antibody concentrations using a commercial ELISA kit with cutoff of 25 mIU/mL, in line with previously published studies.[49,50] The relevance of this cutoff was recently demonstrated, with study participants having anti-VZV antibody concentrations ≥25 mIU/mL showing a higher level of protection than participants with concentrations <25 mIU/mL.[51]

Immunogenicity against MMR also remained high in both groups during the period tested, with ≥90.3% children being seropositive for anti-measles, -mumps, and -rubella antibodies at year 2. The seropositivity rates were comparable to those observed in the control group (V0) of children, who were vaccinated with two doses of the MMR vaccine. This suggests that presence of the varicella antigen in the MMRV vaccine does not affect long-term immunogenicity to the vaccine's MMR antigens. Moreover, the use of the MMRV vaccine decreases the number of vaccinations required to obtain the same level of protection against all four vaccine components. The results of the global study indicated that high seropositivity rates for anti-measles, -mumps, and -rubella antibodies were also observed throughout the study until year 10, regardless of the vaccine schedule administered.[37]

The safety results reported here for each schedule were comparable to those reported in the global study,[36] and support the acceptable safety profiles of both VCVs.[5,20,52] Redness at the injection site and fever were the most frequently reported AEs, in line with previous observations for VCVs.[52] Post-vaccination 1, there was a trend for higher fever rates in children who received one or two doses of VCV compared to children who received no VCV. Such higher rates of fever post-vaccination 1 have been described in a previously published meta-analysis for tetravalent MMRV vaccine compared to trivalent MMR vaccine. This meta-analysis also reported that these higher rates did not trigger more frequent febrile seizures.[52] On the other hand, a large study including more than 400,000 children indicated a higher risk of febrile seizures following vaccination with a tetravalent MMRV vaccine compared to vaccination with the trivalent MMR vaccine together with the monovalent V vaccine.[53] Nevertheless, in the Russian cohort of our study, no cases of meningism (including febrile seizures) were reported in children receiving either study vaccine.

While eight SAEs were considered causally related to vaccination in the global study, including four febrile seizures (three in the V2 group and one in the V0 group),[36] no vaccination-related SAEs or deaths were reported in Russian children. Additionally, no complicated varicella cases were reported in Russian children, or in the global study.[9] Six HZ cases were reported in the global study,[9] but none were reported in Russian children.

The strengths of this study include the long-term follow-up in a large number of children and in settings where VZV is endemic. Moreover, the study design was robust and included several vaccination schedules, with different VCVs, and a thorough confirmation of suspected varicella cases involving clinical assessment, PCR testing, and IDMC ascertainment. Together, these factors contributed to the generalizability of the obtained results.

There are some limitations to this study. First, a limited number of children included in the TVC completed the full study and had efficacy and immunogenicity data available for the entire follow-up period. Nevertheless, the VE sensitivity analysis, which was conducted on the confirmed and probable varicella cases, suggested that the data obtained in the main analysis of this study were robust. Second, no data were available for immunogenicity against MMR in Russian children beyond year 2 because the study was discontinued in regions where varicella vaccination was introduced in the regional immunization program in 2006–2007.[54] However, the global results of this study have been published[37] and are likely generalizable to Russian children given the similar demographic characteristics (e.g., ≥98% of children of white Caucasian heritage).

In conclusion, vaccination against varicella resulted in clear reductions in the incidence of varicella disease in Russian children over 10 years of follow-up, with VE estimates in line with the global study. The highest VE estimate and lowest number of breakthrough cases were observed in children who received the two-dose schedule. Anti-VZV antibodies persisted until year 10 of the follow-up in children who received the one-dose or two-dose schedule, and the acceptable safety and

tolerability profile of both VCVs was confirmed. Therefore, these data add valuable evidence for authorities who consider implementation of UVV in settings, such as the Russian population. The estimated VE against varicella over 10 years of follow-up supports the use of a two-dose varicella vaccination schedule over a one-dose schedule.

Abbreviations

AE	adverse event
ATP	according-to-protocol
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
GMC	geometric mean concentration
HR	hazard ratio
HZ	herpes zoster
IDMC	independent data monitoring committee
IgG	immunoglobulin G
IU	international units
LAR	legally acceptable representative
MMR	measles mumps and rubella
MMRV	measles mumps rubella and varicella
PCR	polymerase chain reaction
SAE	serious adverse event
SAS	Statistical Analysis System
TVC	total vaccinated cohort
USA	United States of America
UVV	universal varicella vaccination
monovalent V vaccine	monovalent varicella vaccine
V0	group of children receiving two doses of the combined trivalent measles mumps and rubella vaccine
V1	group of children receiving one dose of the combined trivalent measles mumps and rubella vaccine followed by one dose of varicella vaccine
V2	group of children receiving two doses of the combined tetravalent measles mumps rubella and varicella vaccine
VCV	varicella zoster virus-containing vaccine
VE	vaccine efficacy
VZV	varicella zoster virus
WHO	World Health Organization

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Authors contributions

All authors attest they meet the ICMJE criteria for authorship. L. Namazova-Baranova, Y. Yakovlev, V. Tatochenko, and V. Romanenko were involved in the conception or the design of the study. All authors, except G. Casabona, M. A. Habib, M. Povey, and L. Namazova-Baranova, participated in the collection or generation of the study data. All authors, except G. Casabona, M. A. Habib, M. Povey performed the study. E. Shpeer, Y. Yakovlev, V. Tatochenko, and I. Ryzhenkova contributed to the study with materials and analysis tools. G. Casabona, M. A. Habib, M. Povey, L. Namazova-Baranova, K. Efendieva, M. Fedoseenko, J. Levina, I. Sidorenko, A. Zhestkov, A. Lyamin, Y. Yakovlev, and V. Tatochenko were involved in the analyses or interpretation of the data. All authors had full access to data and take responsibility for data integrity and accuracy of the data analysis. All authors reviewed the manuscript and gave final approval before submission.

Disclosure of potential conflicts of interest

G. Casabona, M. A. Habib, M. Povey, E. Shpeer, and M. Scherbakov are employees of the GSK group of companies. M. Scherbakov, M. A. Habib, E. Shpeer, and G. Casabona hold shares in the GSK group of companies as part of their employee remuneration. L. Namazova-Baranova, V. Romanenko, V. Tatochenko, O. Reshetko, Y. Kovshirina, K. Efendieva, M. Fedoseenko, J. Levina, I. Ryzhenkova, I. Sidorenko, Y. Yakovlev, A. Lyamin, O. Fedorova, L. Ogorodova and A. Zhestkov have nothing to disclose. T. Ivleva received personal fees from the GSK group of companies, Sanofi Pasteur, Pfizer, and Merck Sharp & Dohme for performing educational lectures. All authors have no non-financial interest to declare.

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Trademark statement

Priorix, Priorix-Tetra, and Varilrix are owned by or licensed to the GSK group of companies. Varivax is a registered trademark of Merck Sharpe & Dohme Corp.

Data sharing statement

The protocol of this study is available at gsk-studyregister.com (ID 100388). GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to *www.clinicalstudydatarequest.com*. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.

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