Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial

Michael Povey, Ouzama Henry, Marianne A Riise Bergsaker, Roman Chlibek, Susanna Esposito, Carl-Erik Flodmark, Leif Gothefors, Sorin Man, Sven-Arne Silfverdal, Mária Štefkovičová, Vytautas Usonis, Jacek Wysocki, Paul Gillard, Roman Prymula

Summary

Background The duration of protection provided by varicella vaccines is unclear. We assessed the 10-year vaccine efficacy of two doses of a combined measles-mumps-rubella-varicella vaccine (MMRV), one live attenuated varicella vaccine (V) dose given after one measles-mumps-rubella vaccine (MMR) dose (MMR+V), versus two MMR doses (control vaccine) for the prevention of confirmed varicella.

Methods This was a phase 3b follow-up of an observer-blinded, randomised, controlled trial. In phase a, children aged 12–22 months (at first vaccination) from Czech Republic (Czechia), Greece, Italy, Lithuania, Norway, Poland, Romania, Russia, Slovakia, and Sweden were randomly assigned by computer-generated randomisation list (3:3:1) to receive two doses of MMRV, one dose of MMR and one dose of varicella vaccine, or two doses of MMR, 42 days apart. Varicella cases were confirmed by detection of viral DNA, or epidemiological link and clinical assessment, by an independent data monitoring committee; disease severity was based on a modified Vázquez scale. Hazard ratios for MMRV and MMR+V versus MMR estimated in the per-protocol cohort using a Cox proportional hazards regression model were used to calculate vaccine efficacy and 95% CI. Serious adverse events were recorded throughout the study in all vaccinated children. Study objectives were secondary and descriptive. The trial is registered at ClinicalTrials.gov, number NCT00226499.

Findings Between Sept 1, 2005, and May 10, 2006, 5803 children (mean age 14·2 months, SD 2·5) were vaccinated. The per-protocol cohort included 2279 children from the MMRV group, 2266 from the MMR+V group, and 744 from the MMR group. From baseline to a median follow-up of 9·8 years, 76 (3%) children in the MMRV group, 469 (21%) in the MMR+V group, and 352 (47%) in the MMR group had varicella. Vaccine efficacy against all varicella was 95·4% (95% CI 94·0–96·4) for MMRV and 67·2% (62·3–71·5) for MMR+V; vaccine efficacy against moderate or severe varicella was 99·1% (97·9–99·6) for MMRV and 89·5% (86·1–92·1) for MMR+V. During phase b, serious adverse events were reported by 290 (15%) of 1961 children in the MMRV group, 317 (16%) of 1978 in the MMR+V group, and 93 (15%) of 641 in the MMR group. There were no treatment-related deaths.

Interpretation The 10-years vaccine efficacy observed, suggests that a two-dose schedule of varicella vaccine provided optimum long-term protection for the prevention of varicella by offering individual protection against all severities of disease and leading to a potential reduction in transmission, as observed in the US experience with universal mass vaccination.

Funding GlaxoSmithKline Biologicals.

Lancet Infect Dis 2019; 19: 287–97

Published **Online** February 11, 2019 http://dx.doi.org/10.1016/S1473-3099(18)30716-3

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on January 29, 2020

See **Comment** page 222

GlaxoSmithKline, Wavre, Belgium (M Povey MSc; P Gillard MD); **GlaxoSmithKline, Rockville, MD, USA** (O Henry MD); **Division of Health Services, Department of Global Health, Norwegian Institute of Public Health, Oslo, Norway** (M A Riise Bergsaker MD); **University of Defence, Faculty of Military Health Sciences, Hradec Kralove, Czech Republic** (Prof R Chlibek MD; Prof R Prymula MD); **Pediatric Clinic, Department of Surgical and Biomedical Sciences, Università degli Studi di Perugia, Perugia, Italy** (S Esposito MD); **Department of Paediatrics, Skånes University Hospital, Malmo, Sweden** (C-E Flodmark MD); **The Public Health Agency of Sweden and Department of Clinical Sciences/Pediatrics, Umeå University, Umeå, Sweden** (L Gothefors MD); **3rd Pediatric Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania** (Prof S Man MD); **Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden** (S-A Silfverdal MD); **Faculty of Health Care, Alexander Dubček University of Trenčín, Trenčín, Slovakia** (M Štefkovičová MD); **Clinic of Children's Diseases, Institute of**

Introduction

After the introduction of universal vaccination of children against varicella using a one-dose schedule in the USA and other countries, the incidence of varicella cases and associated admissions to hospital and deaths substantially declined.[1–4] A two-dose live varicella vaccine schedule was recommended by the USA's Advisory Committee on Immunization Practices in 2007, for the active immunisation of children aged 9 months or older, which further decreased the incidence of varicella.[5] Vaccination schedules could include a monovalent live attenuated varicella vaccine (V), or a combination measles-mumps-rubella-varicella vaccine (MMRV).[5–7] Previous studies have shown comparable antibody responses after dose two, whether this was administered 6–12 weeks or 3–6 years after dose one.[8] Although monovalent varicella vaccine can be given together with other childhood vaccines at separate injection sites, the use of a combined

Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania (Prof V Usonis MD); **Department of Preventive Medicine, Poznan University of Medical Sciences, Poznan, Poland** (Prof J Wysocki MD); **and Charles University, Faculty of Medicine in Hradec Kralove, Department of Social Medicine, Hradec Kralove, Czech Republic** (Prof R Prymula MD)

Correspondence to: Mr Michael Povey, GlaxoSmithKline, Wavre 1300, Belgium
michael.x.povey@gsk.com

Research in context

Evidence before this study

Several countries recommend the universal vaccination of children against varicella using monovalent varicella vaccine (V), given together with other childhood vaccines at separate injection sites, or as a combined measles-mumps-rubella-varicella vaccine (MMRV). A PubMed search on May 15, 2018, of "MMRV" identified three systematic reviews and meta-analyses, among which the most up-to-date was a meta-analysis of the effectiveness, immunogenicity and safety of one-dose versus two-dose varicella vaccination, based on studies published between Jan 1, 1995, and June 30, 2017. The meta-analysis showed that the two-dose varicella vaccination schedule was more immunogenic and more effective at preventing varicella disease than one dose of varicella vaccine. For two doses versus one dose of varicella vaccine, vaccine effectiveness increased by 79% in randomised controlled trials (RCTs), 63% in cohort studies, and 81% in case-control studies. Direct evidence for a protective effect was provided by two RCTs that compared the vaccine efficacy of one-dose and two-dose varicella vaccine schedules. The first RCT to compare the dosing schedules was done before varicella vaccine was licensed in 1995, meaning that disease exposure and transmission was high. In the most recent RCT to provide efficacy data on varicella vaccines, children were enrolled and vaccinated between Sept 1, 2005, and May 10, 2006, in countries with endemic varicella among children and with no recommendation for varicella vaccination. This phase 3 RCT assessed two doses of MMRV or one dose of measles-mumps-rubella vaccine (MMR) + one dose of varicella vaccine (MMR+V) compared with two doses of MMR (control), and at the 3-year follow-up showed that, compared with control vaccine, the efficacy of the two-dose MMRV schedule was 94·9%, the efficacy of the one-dose varicella vaccine schedule was 65·4% against all varicella. The 6-year follow-up showed that, compared with control vaccine, the efficacy of two doses of MMRV against all varicella was 95·0%, and of one dose was 67·0%. These efficacy estimates support the use of two doses of MMRV over the one-dose varicella vaccine schedule for protection against varicella disease for up to 6 years after vaccination in healthy children.

Added value of this study

Further to the analyses at years 3 and 6, this long-term follow-up provides descriptive efficacy estimates for varicella vaccine in children aged 10–11 years. The vaccine efficacy estimates over 10 years showed that compared with control vaccine, for two-dose MMRV the efficacy against all varicella was 95·4%, and for one dose of varicella vaccine was 67·2%. That is, in a setting where varicella is endemic among children allowing for natural boosting, compared with control vaccine, the two-dose MMRV schedule provided higher protection throughout 10 years than one dose of varicella vaccine against all severities of varicella disease.

Implications of all available evidence

The effectiveness of various varicella vaccines for protection against varicella disease in children has been widely established in countries which include varicella in routine childhood vaccination programmes. In addition, the benefits of combined MMRV over separate injections of MMR+V are well established, and include simpler delivery of vaccines, increased compliance, and reduced health-care costs. The clinical evidence shows that a two-dose schedule of live varicella MMRV provides robust long-term protection against varicella disease in young children.

MMRV reduces the number of injections and is reported to improve vaccine uptake.[9,10]

In a previously published phase 3a, randomised, observer-blinded, multicentre study, 5803 children were vaccinated during the second year of life 42 days apart with two doses of MMRV (MMRV group), or one dose of measles-mumps-rubella vaccine (MMR) then one dose of varicella vaccine (V; MMR + V group), or two doses of MMR control vaccine (MMR group).[11] The study was done in countries with endemic varicella among children aged 12–22 months, but without recommendation for the vaccination of children against varicella.

During a mean follow-up of about 3 years, the attack rate in the control group was of 10·4 per 100 person-years (201 events) and 0·6 per 100 person-years (37 events) in the MMRV group.[11] The observed vaccine efficacy against varicella of 94·9% with two doses of MMRV was consistent with previous estimates of vaccine efficacy with two-dose schedules of MMRV (91%) or monovalent varicella vaccine (98%).[12,13] The varicella attack rate in the MMR + V group was 3·8 per 100 person-years (243 events) and the observed vaccine efficacy of 65·4% was consistent with the effectiveness estimate of 72% from a meta-analysis of one-dose monovalent varicella vaccines given during a varicella outbreak.[14]

After completing the 3-year follow-up in phase 3a, children entered phase 3b, which included assessments up to 10 years follow-up. At 6 years (median 6·4 years), the vaccine efficacy for two-dose MMRV was 95·0% against all varicella and 99·0% against moderate or severe varicella, and for MMR + V was 67·0% against all varicella and 90·3% against moderate or severe varicella. In the majority of children, immune responses at 6 years against varicella zoster virus were above the threshold for seroconversion.[15]

The observed vaccine efficacy for protection against all varicella at years 3 and 6 follow-up supported the use of two-dose MMRV over one-dose MMR + V, although it was not known whether the vaccines offered long-term protection or deferred the appearance of moderate or severe disease. In this report from phase b of the study, we describe vaccine efficacy and antibody persistence

against varicella at a median follow-up of 9·8 years after two doses of MMRV or one dose of MMR+one dose of varicella vaccine versus two doses of MMR control. A summary contextualising the outcomes of this study for health-care professionals is presented in the appendix.

Methods

Study design

This phase 3b study was an observer-blind, controlled, assessment of children aged 12–22 months who were randomly assigned (3:3:1) to receive two doses of MMRV, one dose of MMR followed by one dose of V, or two doses of MMR control vaccine, 42 days apart. The study comprised two distinct surveillance periods: phase a and b. Phase a+b began 6 weeks after dose two and ended at the last visit in phase b (year 10), covering the overall 10 years of the study, whereas phase b started, on average, 3 years after vaccination and ended at the last visit in phase b. An overview of the study design is shown in the appendix.

The study was done in Czech Republic (Czechia), Italy, Greece, Lithuania, Norway, Poland, Romania, Russia, Slovakia, and Sweden (NCT00226499). A protocol summary is available. The follow-ups at years 3 and 6 have been previously published.[11,15] Here we describe vaccine efficacy and varicella zoster virus antibody persistence up to 10 years after vaccination.

Participants

Children aged 12–22 months were eligible for inclusion if they had not received MMR or varicella vaccines, or both, or had measles-mumps-rubella or varicella zoster or herpes zoster diseases, or both, and were at home with at least one sibling with negative history of varicella disease and vaccination, at a child-minders where at least one child was without a known positive history of varicella disease and vaccination, playing for more than 5 min/week with children without a known positive history of varicella disease and vaccination, or registered to attend day care from 24 months. All parents and guardians gave informed written consent for participation.

The study was done in accordance with the Declaration of Helsinki and International Harmonization Good Clinical Practice guidelines. The protocol was reviewed and approved by an independent ethics committees or institutional review board in all participating countries. Protocol deviations have been previously published.[11]

Randomisation and masking

The vaccines assessed were MMRV (Priorix-Tetra, GlaxoSmithKline [GSK]), MMR (Priorix, GSK), and monovalent varicella (V; Varilrix, GSK). Randomisation and blinding have been previously described.[11] Briefly, children were randomly assigned (3:3:1) to receive two doses of MMRV at days 0 and 42 (MMRV group); one dose of MMR at day 0 and one dose of varicella vaccine at day 42 (MMR+V group), or two doses of MMR vaccine as control at days 0 and 42.

Procedures

Vaccines were administered subcutaneously in the deltoid of the child's left arm. Three lots each of MMRV and monovalent varicella vaccine and one lot of MMR control vaccine were used. During phase b, the study remained observer blind (including parents and guardians) for all groups except the MMR+V group in countries where the national vaccination schedule includes a second dose of MMR vaccination at age 4–8 years (Czech Republic, Italy, Lithuania, Romania, Russia, and Sweden). The independent data monitoring committee remained masked to the study treatment group when assessing varicella cases.

See **Online** for appendix

Outcomes

The outcomes for phase b were secondary and descriptive. The efficacy outcomes were to assess vaccine efficacy of two doses of MMRV or one dose of MMR+one dose of varicella vaccine versus two doses of MMR control vaccine against varicella at 10 years after vaccination, and vaccine efficacy of MMRV or MMR+V for the prevention of varicella according to the severity of varicella cases. The immunogenicity outcomes at 10 years were to assess the proportions of varicella zoster virus seropositivity, geometric mean titres, and geometric mean concentrations of varicella zoster virus antibodies. Measles, mumps, and rubella antibody titres in a subset of children at years 4, 6, 8, and 10 will be presented elsewhere. The long-term safety outcome was to describe serious adverse events and cases of herpes zoster.

For the **study protocol** see www.gsk-clinicalstudyregister.com/study100388

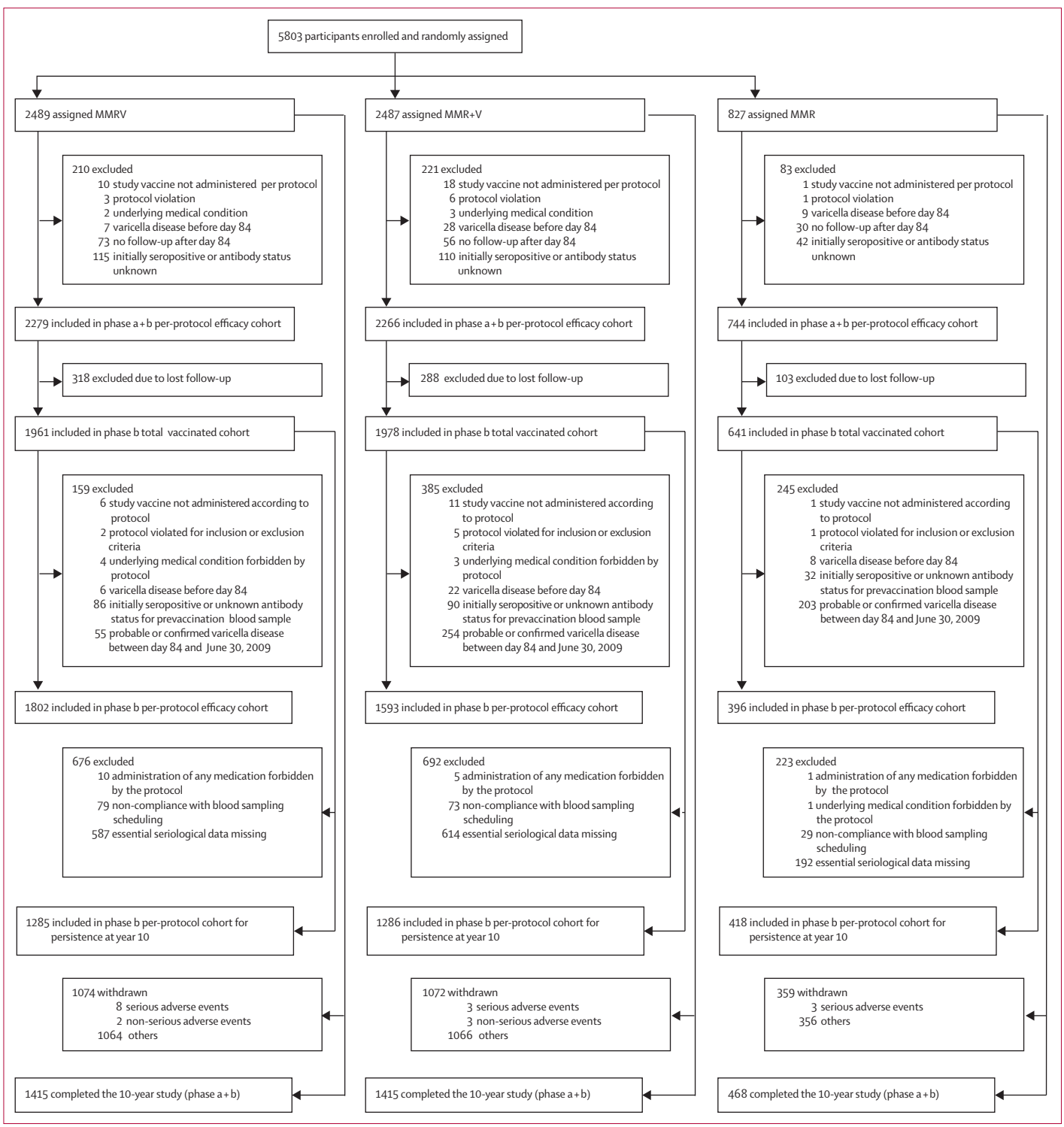
The burden of illness was assessed among parents and guardians who had a child with confirmed varicella, including: time lost from work as a result of caring for their child; time their child lost for daily activities (attendance at daycare, child minders, school, extra-curricular activities); time when assistance was needed to care for their child with varicella (nurse, babysitter, paid caregiver); and whether they would have contacted or visited a physician to seek advice for varicella if their child were not participating in the trial.

Parents were asked to seek assessment if their child or a member of their household had any rash or illness resembling varicella or herpes zoster, and a detailed description of the rash was recorded. The description included duration of rash episode; estimation of the daily number of lesions or vesicles, or both; measurement of daily body temperature during the period of rash; and the date when the illness ended (first day when the child resumed normal everyday activities as it was before the onset of varicella zoster). Vesicular dermal lesions were sampled by unroofing the lesion and collecting the fluid by capillary action. Dry lesions (papules or crusts) were sampled by unroofing and swabbing, or by collecting

scabs or crusts from lesions. The samples were used for the laboratory identification and characterisation of varicella zoster virus. DNA for qualitative and strain identification (wild type or vaccine) was done using PCR-restriction fragment length polymorphism.

Parents and guardians were contacted by telephone once every 6 months during phase b to remind them to report suspicions of varicella or zoster infection in their child.

During the case ascertainment visit, the investigator recorded the date of the visit, examined the child to



describe the case in detail, and photographed the lesions to document their distribution and nature. Collection of biological samples from the dermal lesions for viral identification and recording the number and type of samples were reported in the child's electronic case report form. The verification and transcription of diary card (ie, a card given to the parents or guardians to record characteristics of the suspected varicella illness) data in the child's electronic case report form included any treatment given the child for varicella, any back or abdominal pain observed in the child, and the outcome of the disease when available. Herpes zoster cases were also recorded.

All cases of varicella-like rash identified by the investigator were referred to the independent data monitoring committee for blinded classification using a modified Vázquez scale (mild ≤7, moderately severe 8–15, severe ≥16).[15,16] The variables for assessing the severity of illness were: rash (number and type of lesions), fever, pain back or abdomen complications, and investigator's subjective assessment of the illness. A varicella case was confirmed when it met the clinical case definition and the PCR result was positive for a wild-type varicella virus, or when it met the clinical definition, was confirmed by independent data monitoring committee, and was epidemiologically linked to a valid index case.[17,18] Assessments of antibody persistence and safety are described in the appendix.

Statistical analysis

The sample size and statistical power calculations for vaccine efficacy in phase a have been previously described.[11] Vaccine efficacy estimates in the long-term follow-up were descriptive. The hazard ratios (HRs) for MMRV and MMR+V versus MMR control were estimated by use of a Cox proportional hazards regression model, accounting for individual follow-up time of each child and censored data. The proportional hazard assumptions were verified using Schoenfeld residual plots. Follow-up time for the varicella cases was censored at the rash start date. Vaccine efficacy was calculated as 100x(1–HR), with a two-sided 95% CI. The phase a+b, and phase b per-protocol cohorts for vaccine efficacy included children who completed their vaccinations and fulfilled the protocol requirements. Children with confirmed or probable varicella disease in phase a were excluded from the phase b vaccine efficacy cohort.

The seropositivity proportions for varicella zoster virus antibodies at each timepoint was defined as the proportion of children with antibody titres of at least 25 mIU/mL who were seronegative (titre <25 mIU/mL) prevaccination. Geometric mean concentrations were calculated by taking the anti-log of the mean of the log concentrations for each assay. Antibody titres below the assay cutoff were given an arbitrary value of half the cut-off for geometric mean concentration calculations. For the varicella zoster virus antibody assay, all titres between 25 mIU/mL and 40 mIU/mL were given a value of 25 mIU/mL before log-transformation. Children with missing or non-evaluable measurements were excluded from immunogenicity analyses. Antibody persistence was assessed in the per-protocol cohort for persistence including children who completed their vaccinations, fulfilled the protocol requirements, and had a serum sample at the given timepoint.

All safety assessments were done in the total vaccinated cohort, including all children who received at least one

	MMRV (N=2279)	MMR+V (N=2266)	MMR (control; N=744)
Mean age at vaccine dose one	14·2 (2·5)	14·2 (2·4)	14·2 (2·5)
Girls	1057 (46%)	1109 (49%)	360 (48%)
Boys	1222 (54%)	1157 (51%)	384 (52%)
Race or ethnicity			
White	2227 (98%)	2227 (98%)	737 (99%)
Arabic or north African	21 (1%)	7 (<1%)	2 (<1%)
Other	31 (1%)	32 (1%)	5 (1%)
Country			
Czechia	525 (23%)	516 (23%)	171 (23%)
Greece	115 (5%)	113 (5%)	32 (4%)
Italy	106 (5%)	109 (5%)	35 (5%)
Lithuania	256 (11%)	255 (11%)	86 (12%)
Norway	74 (3%)	76 (3%)	25 (3%)
Poland	385 (17%)	368 (16%)	116 (16%)
Romania	121 (5%)	126 (6%)	42 (6%)
Russia	378 (17%)	392 (17%)	130 (17%)
Slovakia	199 (9%)	195 (9%)	68 (9%)
Sweden	120 (5%)	116 (5%)	39 (5%)
Type of care			
At least one sibling at home	655 (29%)	592 (26%)	192 (26%)
Attending day-care centre	525 (23%)	546 (24%)	187 (25%)
Attending a child minder	148 (6%)	155 (7%)	57 (8%)
At least once a week contact*	2051 (90%)	2055 (91%)	680 (91%)

Data are months (SD) or n (%). Phase a+b was from 6 weeks postvaccination to the final follow-up at year 10. MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine. *With other children without a known positive history of varicella disease or vaccination.

Table 1: **Demographic characteristics in the per-protocol efficacy cohort (phase a+b)**

Figure 1: **Study flowchart**
Children with confirmed or probable varicella disease in phase a were excluded from the phase b vaccine efficacy cohort. Phase a+b was from 6 weeks postvaccination to the final follow-up at year 10. Phase b was from 3 years postvaccination to the final follow-up at year 10. MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine.

	Number of patients (n/N)	Total time to event (years)	Attack rate (95% CI) per 100 person-years	Vaccine efficacy (95% CI)
Phase a+b				
Two-dose MMRV				
All cases	76/2279	16 971	0·4 (0·4–0·6)	95·4% (94·0–96·4)
Moderate or severe	6/2279	17 376	0·0 (0·0–0·1)	99·1% (97·9–99·6)
One-dose MMR+V				
All cases	469/2266	14 567	3·2 (2·9–3·5)	67·2% (62·3–71·5)
Moderate or severe	67/2266	16 918	0·4 (0·3–0·5)	89·5% (86·1–92·1)
MMR (control)				
All cases	352/744	3464	10·2 (9·2–11·3)	NA
Moderate or severe	176/744	4492	3·9 (3·4–4·5)	NA
Phase b				
Two-dose MMRV				
All cases	38/1800	10 080	0·4 (0·3–0·5)	95·9% (94·1–97·1)
Moderate or severe	4/1800	10 237	0·0 (0·0–0·1)	98·7% (96·4–99·5)
One-dose MMR+V				
All cases	225/1591	7961	2·8 (2·5–3·2)	69·8% (62·8–75·5)
Moderate or severe	27/1592	8862	0·3 (0·2–0·4)	90·0% (84·2–93·7)
MMR (control)				
All cases	149/396	1473	10·1 (8·6–11·9)	NA
Moderate or severe	59/396	1880	3·1 (2·4–4·1)	NA

Phase a+b was from 6 weeks postvaccination to the final follow-up at year 10, and phase b was from 3 years postvaccination to the final follow-up at year 10. MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine. NA=not applicable.

Table 2: **Descriptive vaccine efficacy estimates against confirmed varicella in the per-protocol efficacy cohorts**

dose of vaccine in phase a. Safety data were described as number and proportion of children reporting the event with a two-sided 95% CI. SAS (version 9.3, including Proc-StatXact, version 8.1 module) was used for all computations.

This trial is registered with ClinicalTrials.gov, number NCT00226499.

Role of the funding source

The trial was sponsored and designed by GlaxoSmithKline Biologicals but amended with input from an independent data monitoring committee consisting of relevant experts. Investigators generated and reported the data for analysis by GSK statisticians according to a prespecified analysis plan. All authors had complete access to the analysed data (without compromising the trial blinding), participated in the drafting and reviewing of the report, and vouch for the accuracy and completeness of this report. MP, OH, MARB, RC, SE, C-EF, LG, SM, S-AS, MS, VU, JW, PG, and RP had final responsibility for the decision to submit for publication. GlaxoSmithKline Biologicals covered the costs associated with the development and publishing of the manuscript, including writing assistance.

Results

5803 children were enrolled and vaccinated between Sept 1, 2005, and May 10, 2006. Phase a was extended through the first half of 2009, so the median follow-up was about 3 years. Phase b started on July 1, 2009, and the last study visit was on Dec 15, 2016.

In phase a, the total vaccinated cohort comprised 5803 children aged 12–22 months at enrolment, of which 4580 children continued long-term follow-up in phase b. The demographic characteristics of the total vaccinated cohort have been previously published.[11] The per-protocol efficacy cohort (phase a+b) included 5289 children (91% of the total vaccinated cohort for phase a), and the per-protocol efficacy cohort (phase b) included a total of 3791 children (83% of the total vaccinated cohort for phase b). During the 10-year follow-up, 2505 children in the total vaccinated cohort were withdrawn from the study, including 14 that withdrew because of a serious adverse event and five because of a non-serious adverse event (figure 1).

The main reasons for exclusion from the per-protocol efficacy cohort (phase a+b) were being seropositive or of unknown serostatus at baseline and being lost to follow-up 42 days after vaccination. In the efficacy cohorts, the demographic characteristics and the level of varicella zoster virus exposure based on care type were balanced across groups, and consistent with the total vaccinated cohort. In the per-protocol efficacy cohort (phase a+b) the mean age of children at enrolment was 14·2 months, 98% of children were white, and most were from Czech Republic (23%), Russia (17%), and Poland (16%, table 1). The per-protocol persistence cohort included 5235 children (90% of the total vaccinated cohort; appendix). The main reasons for exclusion from the per-protocol persistence cohort were blood sample missing, unknown antibody status prevaccination, and being seropositive prevaccination.

In the per-protocol efficacy cohort (phase a+b), during a median 9·8 years of follow-up, contact with varicella or herpes zoster, or both, was reported in 825 (36%) children in the MMRV group, 789 (35%) children in the MMR+V group, and 224 (30%) children in the MMR control group. Varicella cases were recorded in 76 (3%) children in the MMRV group, 469 (21%) in the MMR+V group, and 352 (47%) in the MMR control group. The vaccine efficacy of two doses of MMRV against all varicella cases was 95·4% (95% CI 94·0–96·4) and against moderate or severe varicella was 99·1% (97·9–99·6). The vaccine efficacy of one dose of varicella vaccine in the MMR+V group against all cases was 67·2% (62·3–71·5) and against moderate or severe varicella was 89·5% (86·1–92·1; table 2). A sensitivity analysis done on the total vaccinated cohort revealed similar vaccine efficacy to that observed in the per-protocol efficacy cohort (data not shown). Over the 10-year follow-up, annual vaccine efficacy remained more than 91·4% for MMRV and more than 59·4% for MMR+V and were stable over time (figure 2). The mean severity scores of the first confirmed varicella cases were 4·9 (SD 2·0) in the MMRV group and 5·4 (2·3) in the MMR+V group. In the MMR control group, the mean

severity score was 7·7 (3·1; appendix). No cases of severe confirmed varicella were reported in the MMRV group, one severe confirmed case in the MMR+V group (<1%), and six severe cases in the MMR control group (1%).

Among the children who developed varicella disease in the MMRV and MMR+V groups during the follow-up period, the majority had 50 lesions or fewer (MMRV 88%, MMR+V 76%). By comparison, 36% of those with confirmed varicella disease in the MMR control group exhibited one to 50 lesions and the majority had more than 50 lesions (32% with 51–100 lesions, 28% with 101–500 lesions, and 4% with >500 lesions). The monthly distribution of confirmed varicella cases showed higher proportions of varicella cases in the autumn, winter, and spring, compared with summer, with almost no cases reported in August. This seasonal distribution is clear in the MMR control group and MMR+V group, but less so in the MMRV group because of the very low number of reported cases (appendix).

In the per-protocol efficacy cohort (phase b), the median duration of follow-up was 6·59 years in the MMRV group, 6·57 years in the MMR+V group, and 6·55 years in the MMR group. Contact with varicella cases, herpes zoster cases, or both, was reported in 404 (22%) children in the MMRV group, 348 (22%) children in the MMR+V group, and 77 (19%) children in the MMR control group. Confirmed varicella cases were recorded in 38 (2%) children in the MMRV group, 225 (14%) in the MMR+V group, and 149 (38%) in the MMR control group. The vaccine efficacy of two-dose MMRV against all varicella was 95·9% (95% CI 94·1–97·1) and against moderate or severe varicella was 98·7% (96·4–99·5). The vaccine efficacy of one-dose MMR+V against all varicella was 69·8% (62·8–75·5) and against moderate or severe varicella was 90·0% (84·2–93·7; table 2). For both groups, efficacy against probable varicella cases was similar to that observed for confirmed cases (data not shown). The mean severity scores of first confirmed varicella cases were 5·0 (SD 2·4) in the MMRV group, 5·1 (2·2) in the MMR+V group, and 7·2 (3·2) in the MMR control group (appendix).

In the per-protocol persistence cohort, two doses of MMRV, and one dose of MMR+V induced varicella zoster virus antibody responses that persisted for up to 10 years after vaccination, with geometric mean concentrations at least five-times greater than the threshold for seropositivity (25 mIU/mL) at all timepoints assessed, with and without censoring post-infection data. At 10 years, the proportion of seropositive children was 99·6% in the two-dose MMRV groups and 98·4% in the one-dose MMR+V group (figure 3). In the MMRV and MMR+V groups, geometric mean concentrations for varicella zoster virus antibodies increased gradually from 1–10 years follow-up, and at 10 years, geometric mean concentrations were similar in both groups, and greater than 16-times higher than the threshold for seropositivity. In the MMR control group, 8·4% of children were seropositive for varicella zoster virus antibodies at 1 year; geometric mean concentrations for varicella zoster virus antibodies increased at all timepoints from 1 year, and the proportion of seropositive children at years 2, 4, 6, 8, and 10 were 13·6%, 30·2%, 55·1%, 66·7%, and 73·0%, respectively.

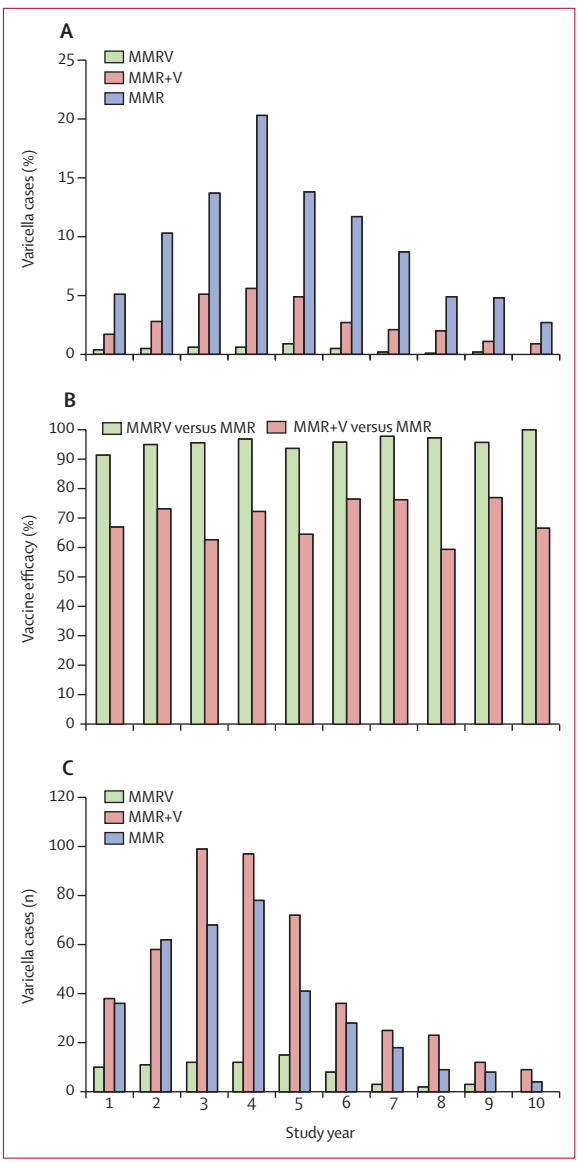


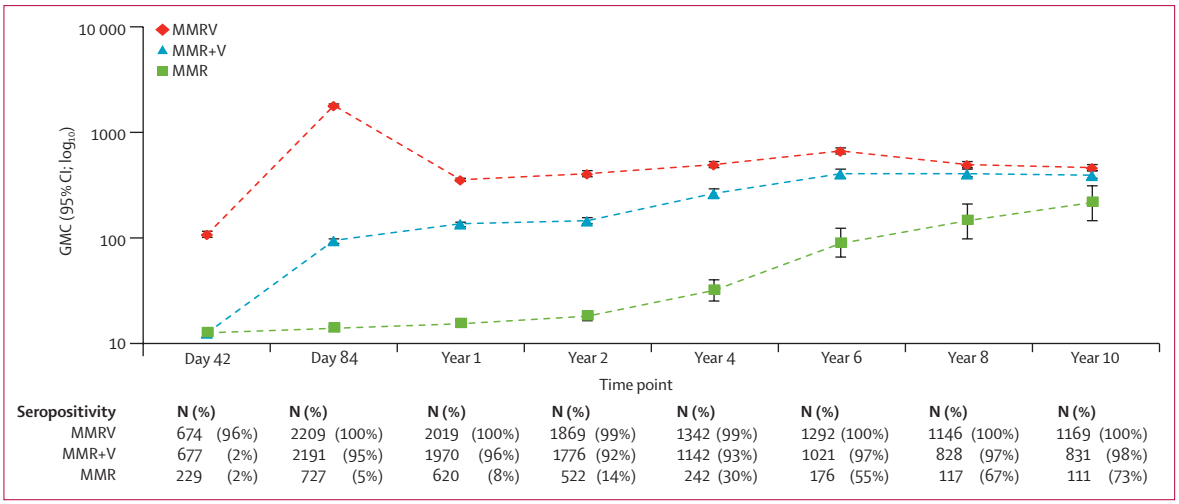
Figure 2: **Percentage of children with a confirmed varicella case (A), vaccine efficacy against all varicella (B), and number of varicella cases (C) by year in the per-protocol cohort for efficacy**
MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine.

In the total vaccinated cohort during phase a+b, a total of 2694 serious adverse events were reported for 1538 children, of which none were complicated varicella cases; eight serious adverse events were considered vaccine-related by the investigator (table 3). In phase a, 57% of children in the MMRV group, 45% in the

MMR+V cohort, and 40% in the MMR cohort reported fever of at least 38°C within 15 days of the first dose. In phase a, two of the serious adverse events were fatal but not considered vaccine-related by the investigator (one accidental death due to a fire, and one accidental death due to a television set [mechanical fault]). Reactogenicity and safety during phase a has been previously reported.[11] In the total vaccinated cohort, during phase b, at least one serious adverse event was reported by 290 (15%) children in the MMRV, 317 (16%) in the MMR+V group, and 93 (15%) in the MMR control group. During phase a+b, 14 children withdrew from the study because of a serious adverse event. None of the serious adverse events reported in phase b were considered vaccine-related by the investigator, and none were fatal.

In the total vaccinated cohort during phase a+b, there were six confirmed cases of herpes zoster (four children in the MMR+V group and two children in the MMR group), all of which were mild. Five children tested positive for the wild-type virus and the other was negative by PCR (appendix). Two children in the MMR+V group and one in MMR group had papular lesions. Two children in MMR+V group and one child in MMR group had vesicular lesions.

Among parents and guardians of children with confirmed varicella infection, 41·6% (95% CI 30·4–53·4),



Seropositivity	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
MMRV	674 (96%)	2209 (100%)	2019 (100%)	1869 (99%)	1342 (99%)	1292 (100%)	1146 (100%)	1169 (100%)
MMR+V	677 (2%)	2191 (95%)	1970 (96%)	1776 (92%)	1142 (93%)	1021 (97%)	828 (97%)	831 (98%)
MMR	229 (2%)	727 (5%)	620 (8%)	522 (14%)	242 (30%)	176 (55%)	117 (67%)	111 (73%)

Figure 3: **Varicella zoster virus antibody persistence in the per-protocol persistence cohort**
MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine. GMC=geometric mean antibody concentration.

	Sex	Country	Race	Age at onset (years)	Verbatim	Preferred term	Primary System Organ Class	Type of medical attendance	Dose	Day of onset	Duration (days)	Outcome
MMRV	Female	Greece	White	1	Febrile convulsions	Febrile convulsion	Nervous system disorders	HO	1	9	1	Recovered or resolved
MMR+V	Female	Greece	White	1	Papular rash linear	Herpes zoster	Infections and infestations	MD	1	24	36	Recovered or resolved
MMR+V	Female	Greece	White	1	Papular vesicular rash	Rash papular	Skin and subcutaneous tissue disorders	MD	1	16	10	Recovered or resolved
MMR+V	Male	Sweden	White	1	Peritonsillar abscess	Peritonsillar abscess	Infections and infestations	HO	2	6	21	Recovered or resolved
MMRV	Male	Poland	White	1	Febrile convulsions	Febrile convulsion	Nervous system disorders	HO	1	8	1	Recovered or resolved
MMR+V	Female	Norway	White	1	Suspected secondary bacterial infection of varicella lesion	Bacterial infection	Infections and infestations	MD	2	3	13	Recovered or resolved
MMRV	Male	Sweden	White	1	Fever conculsion	Febrile convulsion	Nervous system disorders	MD	1	8	1	Recovered or resolved
MMR	Male	Poland	White	1	Febrile seizures	Febrile convulsion	Nervous system disorders	HO	1	8	1	Recovered or resolved

MMRV=measles-mumps-rubella-varicella vaccine. MMR+V=live attenuated varicella vaccine after MMR. MMR=measles-mumps-rubella vaccine. HO=admitted to hospital. MD=medical personnel.

Table 3: **Overview of serious adverse events related to vaccination in the total vaccinated cohort from day 0 to 10-years follow-up**

40·7% (36·3–45·3), and 44·1% (38·8–49·4) of the MMRV, MMR+V, and MMR control groups reported losing time from work as a result of their child's illness. The median time lost from work was 27 h in the MMRV group, 40 h in the MMR+V group, and 48 h in the MMR control group (appendix). The median time lost from planned activities, such as nursery, school, or day care reported by parents of children with confirmed varicella infection was 36 h in the MMRV group, 42 h in the MMR+V group, and 50 h in the MMR control group. The proportion of parents who stated that they would have contacted a physician regarding their child's illness had they not been in a clinical trial was 69% in the MMRV group, 77% in the MMR+V group, and 82% in the MMR control group.

Discussion

In this phase 3b, long-term follow-up of an observer-blind, controlled study of children randomly assigned (3:3:1) to receive two doses of MMRV, one dose of MMR+one dose of varicella vaccine, or two doses of MMR control during the second year of life, we describe the long-term vaccine efficacy for the prevention of varicella and the persistence of varicella zoster virus antibodies. During a median 9·8 years follow-up, the vaccine efficacy of two doses of MMRV against all (probable and confirmed) varicella cases was 95·4% compared with 67·2% with one dose of varicella vaccine. This is consistent with phase a of the study, where at 3 years follow-up, the vaccine efficacy of two doses of MMRV against all varicella cases was 94·9% and for one dose of varicella vaccine was 65·4%. Our 10-year vaccine efficacy estimates suggest that the short two-dose MMRV schedule provided optimum long-term protection for the prevention of all varicella, although both the MMRV and MMR+V schedules were effective, with MMRV preventing moderate or severe varicella at 99·1% and MMR+V at 89·5%.

In phase a, the vaccine efficacy estimates supported the use of the short two-dose MMRV schedule over the one-dose MMR+V schedule, although it was not known whether the vaccines offered long-term protection or delayed the appearance of moderate or severe disease. Previous studies have shown that cases of varicella are milder in severity for children who are vaccinated than for those who are unvaccinated, although the incidence of varicella is reported to increase from 1 year to up to 10 years post vaccination.[19,20] In the MMRV and MMR+V groups, respectively, during the first 3 years of follow-up, the rates of varicella were 0·6 per 100 person-years and 3·8 per 100 person-years, and over the 10 years follow-up period were 0·4 per 100 person-years and 3·2 per 100 person-years. In addition, in phase a, the mean severity scores for cases were indicative of mild disease in the MMRV group at 4·8 (SD 1·5) and MMR+V group at 5·5 (2·1), compared with moderate or severe disease in the MMR control group at 8·1 (2·9).[11] In phase b, the mean severity scores indicated mild disease in the MMRV group at 5·0 (2·4) and MMR+V group at 5·1 (2·2), and no severe cases were reported. In the MMR control group, four severe cases were reported, and the mean severity scores were indicative of moderate disease at 7·2 (3·2). These results suggest that among children vaccinated against varicella in the second year of life, cases were milder than cases in unvaccinated children, and that the rate and severity of varicella disease did not increase with time since vaccination up to 10 years follow-up.

In the per-protocol persistence cohort, antibody titres against varicella zoster virus persisted at 10 years, with more than 98% of children in the MMRV and MMR+V groups remaining seropositive. In an environment with endemic varicella, some vaccinees might experience subclinical disease in the early years after vaccination, which might boost varicella zoster virus-specific immune responses and re-establish protection. This exogenous boosting was considered to have contributed to the high vaccine effectiveness in the early years after mass vaccination against varicella was implemented in the USA.[21] Seropositivity proportions at day 84 were 99·8% in the MMRV group and 95·0% in the MMR+V group, with no change at 2 years (MMRV 99·4%, MMR+V 92·3%), suggesting that natural exposure to varicella zoster virus had no exogenous boosting effect of humoral immune responses during the 2 years after vaccination. At 10 years, the proportions of children who were seropositive for varicella zoster virus (≥25 mIU/mL) were 99·6% in the MMRV group and 98·4% and MMR+V group, and the proportions of children with varicella zoster virus titres of at least 50 mIU/mL were 98·0% and 93·7%, respectively, suggesting that long-term natural exposure to varicella zoster virus had a modest boosting effect in the one-dose MMR+V group.

The previously reported safety profiles of the vaccines during the follow-up at 2 years were consistent with the established profile of combined MMRV and monovalent live attenuated varicella vaccines.[22–25] Within 15 days of dose one, fever of 38°C or more and grade 3 fever were more frequent in the MMRV group than the other vaccine groups, which is in line with various studies that have reported an increased risk of febrile seizures after the first dose of MMRV compared with separate MMR+V, although the risk is relatively low.[7,26–29] Our study was not powered to detect increased risk of febrile seizures. From the start of phase b to 10 years post vaccination, the proportions of serious adverse events were similar between the vaccine groups (14·5–16·0%), and none of the serious adverse events were considered vaccine-related by the investigator. During phase a+b, 14 children withdrew from the study because of a serious adverse event, including leukaemia, rhabdomyosarcoma, lymphadenopathy, and thrombocytopenia. Over the 10 years follow-up, no new safety concerns were identified

among children who received two doses of MMRV or one dose of MMR+V.

During the one-dose varicella vaccination era in the USA (1996–2005), the incidence of varicella cases decreased by about 90%, hospitalisation for varicella disease by 88%, and deaths due to varicella disease decreased by more than 65%, when compared with 1995. Further declines in varicella incidence and related hospitalisations have been observed since switching to the two-dose schedule in 2006. The proportion of cases of varicella reported in children with immunocompromising conditions also decreased significantly in the two-dose era when compared with the one-dose era.[30] The rapid implementation of vaccination against varicella in other countries, including Uruguay, Australia, Canada, and Germany, has also shown a substantial decrease in the incidence and severity of varicella infections in children.[1–3,31] However, because varicella is usually perceived as a mild disease in children, vaccination is not a priority for many state-funded programmes, even though mild cases represent an economic burden due to the disruption of a child's activities, reduced work productivity among parents and guardians, and the use of health-care services.[31] In countries that have adopted vaccination against varicella, routine childhood vaccination is reported to be cost-effective from a health-care perspective and a societal perspective.[31]

In each of the vaccine groups in our study, about 40% of parents and guardians of children with confirmed varicella reported losing time from work and about 75% reported that their child missed regular activities such as nursery or school. In the MMRV and MMR+V groups, respectively, parents and guardians lost a mean of 37 h and 42 h of work time, and in the MMR control group, a mean of 52 h were lost. Moreover, in each of the vaccine groups, about two-thirds of parents and guardians said they would have contacted a physician had they not been taking part in a clinical trial, suggesting that varicella disease in children is a societal and health-care burden. Given that the incidence of varicella cases across European countries without universal varicella vaccination was recently estimated to be 5·5 million per year, the economic burden of varicella disease is likely to be substantial.[32]

Concerns have been raised[33] regarding the potential effect of vaccination against varicella on the epidemiology of herpes zoster; however, evidence for such an association is scarce.[34] The possible under-reporting of contacts and cases was a limitation of the study. In phase b, for example, the lowest contact rate was reported in the MMR control group, which also had the highest proportion of varicella cases, meaning that it is probable that some parents did not record contacts that resulted in cases. Moreover, varicella zoster virus seropositivity increased at all timepoints in the MMR control group, and among children who remained in the study until the end and reported no varicella case at any point, 73·0% were seropositive for varicella zoster virus. This suggests that varicella cases were either under-reported, or that infections were subclinical. A further limitation was the relatively high attrition rate in the per-protocol populations for efficacy across the timepoints. However, to the best of our knowledge, this study was the first to compare varicella vaccines with a control group in a cohort of children of a uniform age in a setting where varicella zoster virus transmission is endemic. Additional factors that increase the generalisability of the outcomes were the multicentre, international design and long-term follow-up, active surveillance, rigorous case-confirmation procedures, and the blinded adjudication of suspected cases.

In a setting where varicella zoster virus is endemic among children allowing for natural boosting, the two-dose MMRV schedule provided optimum protection against all severities of varicella disease at 10 years. This is consistent with the vaccine efficacy of two doses of MMRV and one dose of MMR+one dose of varicella vaccine at 2 years post vaccination.

Contributors

OH 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. MARB, RC, SE, C-EF, LG, SM, S-AS, MS, VU, JW, and RP recruited patients. All authors contributed to the interpretation of data and the drafting of the manuscript. They revised it critically for important intellectual content and approved the version to be published.

Declaration of interests

OH, MP, and PG are employed by the GSK group of companies. OH and PG also hold shares in the GSK group of companies as part of their employee remuneration. LG received personal fees from the GSK group of companies for his participation as principal investigator during the study. SM received personal fees from the GSK group of companies for his participation as principal investigator during the study and also speaker fees. SE reports having received personal fees from the GSK group of companies, Sanofi Aventis, Merck, and Vifor outside the submitted work. Honorarium was paid by the GSK group of companies to S-AS's institution of employment for advisory board meetings. MŠ received personal fees from the GSK group of companies for her participation as a principal investigator during the study and also for consultancy and scientific meeting attendance. JW received personal fees from the GSK group of companies for his participation as principal investigator during the study. RP received grants from the GSK group of companies during the study and also grants from the GSK group of companies, Sanofi Pasteur, and Novartis outside the submitted work. All other authors declare no potential competing interests.

Data sharing statement

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Acknowledgments

The authors thank the children who participated in the study and their parents or guardians and the Adjudication Committee. The authors also thank Adrian Kremer (XPE Pharma & Science, Belgium c/o GSK) for publication management, and Annick Moon (Freelancer for XPE Pharma & Science c/o GSK) and the XPE writing platform for drafting the manuscript.

References

1 Lopez AS, Zhang J, Brown C, Bialek S. Varicella-related hospitalizations in the United States, 2000–2006: the 1-dose varicella vaccination era. *Pediatrics* 2011; **127:** 238–45.

2 Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. *Pediatrics* 2008; **122:** e744–51.

3 Quian J, Ruttimann R, Romero C, et al. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997–2005. *Arch Dis Child* 2008; **93:** 845–50.

4 Yin M, Xu X, Liang Y, Ni J. Effectiveness, immunogenicity and safety of one vs. two-dose varicella vaccination: a meta-analysis. *Expert Rev Vaccines* 2018; **17:** 351–62.

5 Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; **56:** 1–40.

6 Ma SJ, Li X, Xiong YQ, Yao AL, Chen Q. Combination measles-mumps-rubella-varicella vaccine in healthy children: a systematic review and meta-analysis of immunogenicity and safety. *Medicine* 2015; **94:** e1721.

7 Ma SJ, Xiong YQ, Jiang LN, Chen Q. Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: a systematic review and meta-analysis. *Vaccine* 2015; **33:** 3636–49.

8 European Centre for Disease Prevention and Control. Varicella vaccination in the European Union. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Varicella-Guidance-2015.pdf (accessed July 10, 2018).

9 Priorix summary of product characteristics. GlaxoSmithKline UK, Stockley Park West, Uxbridge, Middlesex, UB11 1BT. 2017. https://www.medicines.org.uk/emc/medicine/2054 (accessed Aug 18, 2017).

10 Varilrix summary of product characteristics. GlaxoSmithKline UK, Stockley Park West, Uxbridge, Middlesex, UB11 1BT. 2017. https://www.medicines.org.uk/emc/medicine/9787 (accessed Aug 18, 2017).

11 Prymula R, Bergsaker MR, Esposito S, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. *Lancet* 2014; **383:** 1313–24.

12 Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis* 2011; **203:** 312–15.

13 Spackova M, Wiese-Posselt M, Dehnert M, Matysiak-Klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. *Vaccine* 2010; **28:** 686–91.

14 Bayer O, Heininger U, Heiligensetzer C, von Kries R. Metaanalysis of vaccine effectiveness in varicella outbreaks. *Vaccine* 2007; **25:** 6655–60.

15 Henry O, Brzostek J, Czajka H, et al. 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. *Vaccine* 2018; **36:** 381–87.

16 Vazquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med* 2001; **344:** 955–60.

17 Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. In: Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds. The pink book. 11th edn. Washington DC: Public Health Foundation, 2002.

18 Jumaan A, Hughes H, Schmid S, et al. Varicella vaccine-preventable disease surveillance manual. 3rd edn. Atlanta, GA, USA: Centers for Disease Control. 2002; 1–21.

19 Zhang X, Yan Y, Liu F, et al. The epidemiology and risk factors for breakthrough varicella in Beijing Fengtai district. *Vaccine* 2012; **30:** 6186–89.

20 Kurugol Z, Halicioglu O, Koc F, Koturoglu G, Aksit S. Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey. *Int J Infect Dis* 2011; **15:** e475–80.

21 Goldman GS. Universal varicella vaccination: efficacy trends and effect on herpes zoster. *Int J Toxicol* 2005; **24:** 205–13.

22 Dhillon S, Curran MP. Live attenuated measles, mumps, rubella, and varicella zoster virus vaccine (Priorix-Tetra). *Paediatr Drugs* 2008; **10:** 337–47.

23 Goh P, Lim FS, Han HH, Willems P. Safety and immunogenicity of early vaccination with two doses of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine in healthy children from 9 months of age. *Infection* 2007; **35:** 326–33.

24 Knuf M, Habermehl P, Zepp F, et al. Immunogenicity and safety of two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. *Pediatr Infect Dis J* 2006; **25:** 12–18.

25 Kreth HW, Lee BW, Kosuwon P, et al. Sixteen years of global experience with the first refrigerator-stable varicella vaccine (Varilrix). *BioDrugs* 2008; **22:** 387–402.

26 Bauchau V, Van Holle L, Cohen C. Modelling hospitalisation ratios for febrile convulsions and severe varicella under combined measles, mumps, rubella, and varicella (MMRV-Priorix-Tetra) compared to separate MMR + V vaccination. *Drug Saf* 2015; **38:** 1095–102.

27 Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics* 2010; **126:** e1–8.

28 Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR + V vaccination. *Vaccine* 2014; **32:** 645–50.

29 Macartney K, Gidding HF, Trinh L, et al. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. *JAMA Pediatr* 2017; **171:** 992–98.

30 Bialek SR, Perella D, Zhang J, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. *Pediatrics* 2013; **132:** e1134–40.

31 Wutzler P, Bonanni P, Burgess M, Gershon A, Safadi MA, Casabona G. Varicella vaccination—the global experience. *Expert Rev Vaccines* 2017; **16:** 833–43.

32 Riera-Montes M, Bollaerts K, Heininger U, et al. Estimation of the burden of varicella in Europe before the introduction of universal childhood immunization. *BMC Infect Dis* 2017; **17:** 353.

33 Gidding HF, Brisson M, Macintyre CR, Burgess MA. Modelling the impact of vaccination on the epidemiology of varicella zoster virus in Australia. *Aust N Z J Public Health* 2005; **29:** 544–51.

34 Papaloukas O, Giannouli G, Papaevangelou V. Successes and challenges in varicella vaccine. *Ther Adv Vaccines* 2014; **2:** 39–55.