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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REGULAR ARTICLE

Randomised controlled trial showed long-term efficacy, immunogenicity and safety of varicella vaccines in Norwegian and Swedish children

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Abstract

Aim: Several countries, such as Norway and Sweden, have not implemented universal varicella vaccination. We present data for Norway and Sweden that were generated by a paediatric multi-country Phase III study over a 10-year period. This assessed the efficacy, antibody persistence and safety of two varicella vaccines containing the same Oka strain.

Methods: This was an observer-blind, controlled trial conducted in 10 European countries. Children aged 12–22 months (n = 5803) were randomised 3:3:1 and vaccinated between 1 September 2005 and 10 May 2006. The two-dose group received two tetravalent measles-mumps-rubella-varicella vaccine doses. The one-dose group received one monovalent varicella vaccine dose after a measles-mumps-rubella vaccine dose. Control group participants received two measles-mumps-rubella vaccine doses. Main study outcomes were vaccine efficacy against confirmed varicella cases and incidence of adverse events.

Results: Vaccine efficacy in the two-dose group was ≥92.1% in both Norwegian and Swedish children compared to 72.3% in Norway and 58.0% in Sweden in the one-dose group. Incidences of adverse events and serious adverse events were similar in the Norwegian and Swedish study populations.

Conclusion: Consistent with overall study results, high efficacy against varicella and acceptable safety profiles of the two varicella vaccines were observed in Norwegian and Swedish populations. These findings highlight the benefits of varicella vaccines, particularly when administered as a two-dose schedule.

KEYWORDS
efficacy, Norway, safety, Sweden, varicella vaccine

Abbreviations: CI, confidence interval; HR, hazard ratio; MMR, measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine; VZV, varicella-zoster virus.

1 | INTRODUCTION

The varicella-zoster virus (VZV) causes varicella, commonly known as chickenpox, which is a highly contagious disease mainly affecting children. Although the disease is generally mild, potentially severe complications can occur. Varicella may be life-threatening in unprotected foetuses and neonates and in immunocompromised individuals.[1,2] Moreover, VZV may reactivate later in life, resulting in herpes zoster, also known as shingles.[3]

In temperate climates and in the absence of varicella vaccination, more than 90% of children are infected with VZV by the age of 15 years.[4] Varicella is a burden for families as it disrupts the children's activities and reduces the work productivity of parents and guardians. More severe forms of the disease also require healthcare services.[5]

Previous estimates indicate that yearly varicella cases closely correspond to the number of children born each year,[6] which is around 60,000 in Norway and 110,000 in Sweden.[7,8] In these countries, it results in estimated varicella-associated hospitalisation rates of 7.3/100,000 population in Norway and 3.56/100,000 in Sweden. The highest incidences of hospitalisation have been observed for children under the age of one year.[7–9] Seroprevalence of VZV in Swedish children is 98% for children aged 9–12 years, which is comparable to that in other European countries. In Norway, this is slightly lower, at 81.4% for children aged 10–14 years.[7,10]

Currently licenced varicella vaccines in the European Union include two tetravalent measles-mumps-rubella-varicella vaccines (MMRV): Priorix-Tetra (GSK) and ProQuad (Merck Sharp & Dohme Corp). They also include two monovalent varicella vaccines: Varilrix, (GSK) and Varivax (Merck Sharp & Dohme Corp). Universal varicella vaccination programmes have shown great promise in decreasing the incidence and severity of the disease, both directly and through herd immunity. Thereby, they reduce the economic impact of endemic varicella infections.[11] In addition, universal varicella vaccination is of great interest for high-risk populations,[2] particularly when immunisation occurs before immunosuppressive treatment initiation.

In Europe, universal varicella vaccination is recommended in 12 countries: Andorra, Austria, Cyprus, Czech Republic, Finland, Germany, Greece, Hungary, Italy, Latvia, Luxembourg and Spain. It is also publicly funded in Finland, Germany, Greece, Hungary, Latvia, Luxembourg, Italy and Spain.[11–13] However, several countries do not consider universal varicella vaccination as a priority for national immunisation programmes. This is mostly due to the cost of their implementation and the generally mild nature of the disease. In addition, concerns exist that vaccination of children could result in increased varicella and herpes zoster in more vulnerable individuals.[14] In Norway and Sweden, varicella vaccination is not offered through childhood programmes, and the numbers of varicella vaccinations are negligible.[7,8] Furthermore, lack of epidemiological data at the country level may be another factor underlying national decisions not to implement universal varicella vaccination.

To assess the impact of varicella vaccination in Europe, a clinical trial conducted in 10 European countries assessed the efficacy, immunogenicity and safety of two varicella vaccines containing the same Oka strain over a 10-year follow-up period. MMRV was given according to a two-dose schedule, while the monovalent varicella vaccine was administered as a single dose. Results at the European level of the study showed a 95.4% vaccine efficacy against all varicella for two MMRV doses. Vaccine efficacy for one dose of the monovalent varicella vaccine was 67.2% at the end of the 10-year follow-up.[15] Vaccine efficacy against moderate or severe varicella cases was 99.1% and 89.5% for the two-dose and one-dose schedules respectively.[15] In addition, both schedules showed acceptable safety profiles,[15] supporting the European-level long-term benefits of varicella vaccination, particularly when given according to a two-dose schedule. However, many factors, such as societal and cultural differences, recommended vaccination programmes and attitude towards vaccination, can affect vaccine effectiveness in individual countries.[14] Here, we report the efficacy, immunogenicity persistence and safety results in Norwegian and Swedish children, generated in the context of this European study.

A summary contextualising the outcomes of this publication is displayed in the Plain Language Summary (Figure 1).

Key notes

- Varicella vaccine efficacy in Norwegian and Swedish children was previously unknown, and we estimated it by analysing data from a 10-country randomised Phase III study involving 5803 children.
- Schedules consisting of one or two varicella-containing vaccine doses had acceptable safety profiles and reduced the incidence of varicella cases over 10 years of follow-up, with a higher vaccine efficacy observed for the two-dose schedule.
- Our findings highlight the benefits of varicella vaccines, particularly when administered as a two-dose schedule.

2 | PATIENTS AND METHODS

2.1 | Study design

This Phase III randomised, controlled, observer-blind, multi-centre study was conducted with children from 10 European countries. Participants were randomised 3:3:1 in the two-dose, one-dose and control groups respectively. The two-dose group received two MMRV doses. The one-dose group received one monovalent varicella vaccine dose after a measles-mumps-rubella vaccine (MMR) dose. Control group participants received two MMR vaccine doses (Figure 2).[15] The study was carried out in accordance with the Declaration of Helsinki and International Conference of Harmonization Good Clinical Practice. It is registered on clinicaltrials.gov under NCT00226499. The protocol was approved by an independent ethics committee or institutional review board in all participating countries. Parents or legally acceptable representatives provided written informed consent prior to study procedures.

Plain Language Summary

What is the context?

- Varicella is a common childhood disease caused by the highly contagious varicella-zoster virus.
- Routine use of varicella vaccination with either monovalent or combined varicella-containing vaccines, have led to a significant decrease in varicella disease severity and burden.
- A large clinical trial conducted in ten European countries assessed the efficacy and safety of one dose of monovalent varicella vaccine or two doses of combined mumps-measles-rubella-varicella vaccine.

What is new?

- The enrolled children were followed up for a 10-year period to evaluate the persistence of the immune response and the long-term efficacy and safety of the vaccine. Here, we present the results obtained for children in Norway and Sweden.
- We found that:
  - The two-dose vaccination schedule resulted in a higher vaccine efficacy — 92.1% in Norwegian and 92.6% in Swedish children — than the one-dose schedule — 72.3% in Norwegian and 58.0% in Swedish children.
  - The immune response conferred by the vaccines persisted up to 10 years post-vaccination, with at least 90% and at least 83% of children seropositive post-vaccination in Norway and Sweden, respectively.
  - No safety concerns were raised.

What is the impact?

- The results provide valuable information about the benefits of varicella-containing vaccines, particularly when administered following a two-dose schedule.
- They may support the implementation of varicella vaccination in routine immunisation programmes in Norway and Sweden.

FIGURE 1 Plain language summary

2.2 | Study objectives

The present sub-study with Norwegian and Swedish children had three objectives (Figure 2). The first one was to assess vaccine efficacy against confirmed, confirmed or probable, and complicated varicella cases, which were reported as serious adverse events. The second objective was to assess immune response in terms of anti-VZV, anti-measles, anti-mumps and anti-rubella antibody geometric mean concentrations and seropositivity rates. The last objectives were to assess occurrences of solicited local and general adverse events, unsolicited adverse events and serious adverse events, including herpes zoster.

Here, we report descriptive data obtained for Norway and Sweden for the whole duration of the European study, consisting of Phases A and B (Figure 2).

2.3 | Study population

The participants were healthy children aged 12–22 months at the time of the first vaccination. They were regularly exposed to other children through their family situation, attendance to a day care centre or childminder or other activities. Children with any known positive history of mumps, measles, rubella and varicella disease or vaccination could not participate.[15]

2.4 | Study vaccines

The administered MMRV was Priorix-tetra (GSK), and the administered monovalent varicella vaccine was Varilrix (GSK), both containing the same live-attenuated Oka VZV strain. The MMR used

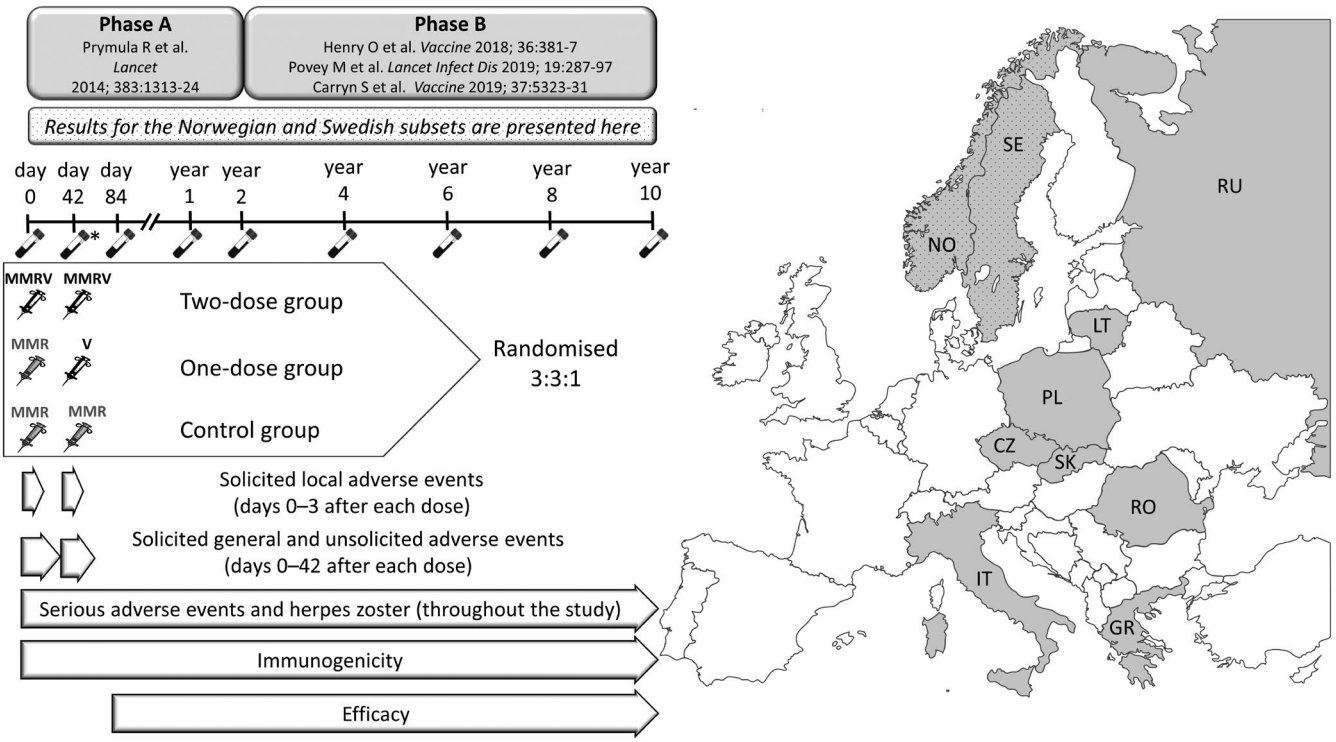


FIGURE 2 Study design. Two-dose, participants having received two doses of measles-mumps-rubella-varicella vaccine; one-dose, participants having received one dose of measles-mumps-rubella vaccine and one dose of varicella vaccine; control, participants having received two doses of measles-mumps-rubella vaccine; MMR; measles-mumps-rubella vaccine; MMRV, tetravalent measles-mumps-rubella-varicella vaccine; V, monovalent varicella vaccine. Solicited local adverse events included redness, swelling and pain. Solicited general adverse events included temperature/fever, rash/exanthem, parotid/salivary gland swelling and suspected signs of meningism. *Only in the subset for measles-mumps-rubella testing

in the control group of this study was Priorix (GSK). Three lots of MMRV and monovalent varicella vaccine and one MMR lot were used. Vaccines were administered subcutaneously in the left deltoid region.

2.5 | Assessments

Varicella case adjudication was performed by an independent data monitoring committee,[15] as described in Appendix S1.

Anti-VZV, anti-measles, anti-mumps and anti-rubella antibody concentrations were assessed by enzyme-linked immunosorbent assay using Enzygnost (DiaSorin) and were expressed in milli-international units per mL (mIU/mL). Sampling time points are summarised in Figure 2.

The time periods for collecting safety-related outcomes are also presented in Figure 2. Consecutive daily monitoring was performed by parents or guardians and reported to the investigators if an event occurred. All visits included questioning about events. When visits were more than 6 months apart, half-yearly telephone interviews were performed to ensure best possible monitoring and reporting.

All solicited local adverse events were considered causally linked to vaccination. Solicited adverse events were graded one to three according to their intensity. The only exception was rash, which was graded from 1 to 4.[16] Grading is described in Table S1, Appendix S2. Severity and causal association of unsolicited adverse events and serious adverse events with study vaccinations were assessed according to the investigator's clinical judgement.

2.6 | Statistical analyses

Statistical analyses were performed using the Statistical Analysis Systems software version 9.3 (SAS Institute Inc).

The incidence rates and vaccine efficacy for Phases A+B were calculated in the according-to-protocol cohort for efficacy, which included children who completed their vaccinations and fulfilled the protocol requirements. Notable exclusion reasons from this cohort were seropositivity for anti-VZV antibodies or a confirmed varicella case before the start of the efficacy follow-up period. The incidence rate was expressed as the number of confirmed varicella cases per 100 person-years and was reported with its 95% confidence interval (CI). The Cox proportional hazards regression model without adjustments was used to estimate the hazard ratio (HR) of experiencing a varicella event in the one-dose and two-dose groups compared to the control group. Vaccine efficacy was estimated as 100 × (1-HR) and was reported with its 95% CI, calculated in the same regression analysis.

Immunogenicity outcomes were assessed in the adapted according-to-protocol cohort for persistence. This included children

who completed their vaccinations, fulfilled the protocol requirements and had a serum sample taken at a given time point.

Seropositivity thresholds were the respective enzyme-linked immunosorbent assay cut-off values: 25 mIU/mL for anti-VZV, 150 mIU/mL for anti-measles, 231 mIU/mL for anti-mumps and 4 mIU/mL for anti-rubella. Antibody geometric mean concentrations were calculated by taking the anti-log of the mean of the log concentrations. Antibody concentrations below the assay cut-off were given an arbitrary value of half the cut-off for geometric mean concentration calculations. For anti-VZV, all concentrations 25–40 mIU/mL were given a value of 25 mIU/mL before log-transformation. Seropositivity rates and antibody geometric mean concentrations were reported with their 95% CIs.

Safety outcomes were assessed in the total vaccinated cohort, which included all children who received at least one study vaccine dose in Phase A. Safety end points were reported as number and proportion of children who reported the event, with 95% CIs.

3 | RESULTS

3.1 | Study participants

A total of 5803 children were enrolled in the European study between 1 September 2005 and 10 May 2006.[15] The total vaccinated cohort included 204 Norwegian and 304 Swedish children, while the according-to-protocol cohort for efficacy included 175 Norwegian and 275 Swedish children (Figure S1, Appendix S2). Reasons for exclusion from the according-to-protocol cohort for efficacy were similar between study groups in both countries. Most children were excluded from the efficacy analyses due to anti-VZV seropositivity at baseline or a varicella episode before day 84.

Of the 190 Norwegian and 292 Swedish children enrolled in Phase B, 73 and 254, respectively, were included in the according-to-protocol cohort for persistence at year 10 (Figure S1, Appendix S2).

Demographic characteristics were similar between the three groups and comparable between the two countries (Table 1). The mean ages at first study vaccination were 14.6 months in Norway and 15.5 months in Sweden; 53.4% and 53.0% of participants were males in the Norwegian and Swedish cohorts respectively. More than 94.0% of participants were Caucasian in both countries. Contact with other children at least once a week occurred for 65.7% of Norwegian and 75.0% of Swedish children.

3.2 | Efficacy

During the 10-year follow-up period, 49 confirmed varicella cases were reported in the Norwegian cohort and 99 in the Swedish cohort (Table 2). The proportions of confirmed cases were highest in the control groups, at 76.0% and 79.5%, respectively, and lowest in the two-dose groups, at 9.5% and 10.0% respectively. The incidence rates per 100 person-years were 1.2 in the Norwegian and Swedish two-dose groups, 4.1 in Norway and 7.6 in Sweden for the one-dose groups, and 16.4 in Norway and 20.9 in Sweden for the control groups (Table 2).[17]

The vaccine efficacy against confirmed varicella was 92.1% in the two-dose group and 72.3% in the one-dose group in the Norwegian cohort, and 92.6% and 58.0%, in these groups, respectively, in the Swedish cohort (Table 2).

Vaccine efficacy against probable and confirmed varicella was 90.0% in the two-dose group and 70.8% in the one-dose group in the Norwegian cohort, and 86.9% and 60.9%, in these groups, respectively, in the Swedish cohort.

As no complicated varicella cases were reported, the vaccine efficacy against such cases was not assessed.

3.3 | Immunogenicity

At day 84, all children in the two-dose groups and 92.5% of Norwegian and 89.6% of Swedish children in the one-dose groups were seropositive for anti-VZV antibodies (Figure 3). Yearly follow-up showed that seropositivity rates remained stable in these groups in both countries. Anti-VZV antibody concentrations in the two-dose vs. the one-dose group on day 84 were 18.1-fold higher in Norway and 25.5-fold higher in Sweden. The evolution of anti-VZV geometric mean concentrations followed similar trends to the seropositivity rates in both countries (Figure 3).

Immune responses against measles, mumps and rubella are presented in the Appendix S2.

3.4 | Reactogenicity and safety

Injection site redness was the most frequently reported solicited local adverse event after the first vaccination in both countries. After the second vaccination, it was redness in the Norwegian cohort and pain in the Swedish cohort. The incidence of grade three local adverse events was low in both countries. Across the two doses and countries, grade three fever was reported by ≤28.9% of children (Table S1, Appendix S2).

Among the reported unsolicited adverse events for the Norwegian children, two were considered causally related to the study vaccines, both following the first vaccination. One was rhinitis, reported in the two-dose group, and the other was pain, reported in the one-dose group. Vaccine-related unsolicited adverse events in the Swedish cohort were diarrhoea, vomiting, pain, decreased appetite, restlessness, irritability, gastroenteritis, nasopharyngitis, peritonsillar abscess and upper respiratory tract infection.

In Phase A, three, and in Phase B, no serious adverse events were considered causally related to the study vaccines.[15] All three resolved during Phase A. No suspected herpes zoster cases were recorded during the 10-year follow-up period in either the Norwegian or Swedish children.

A detailed description of reactogenicity and safety outcomes in Norwegian and Swedish children is provided in the Appendix S2.

TABLE 1 Demographic characteristics of study participants in Norway and Sweden (total vaccinated cohort)

		Norway				Sweden			
Characteristics	**Category**	**Two-dose *N* = 88**	**One-dose *N* = 87**	**Control* *N* = 29**	**Total *N* = 204**	**Two-dose *N* = 131**	**One-dose *N* = 130**	**Control* *N* = 43**	**Total *N* = 304**
Age in months	Mean (SD)	14.9 (1.4)	14.5 (1.1)	14.1 (1.0)	14.6 (1.2)	15.6 (2.0)	15.5 (2.0)	15.5 (2.0)	15.5 (2.0)
Gender, *n* (%)	Male	49 (55.7)	47 (54.0)	13 (44.8)	109 (53.4)	63 (48.1)	71 (54.6)	27 (62.8)	161 (53.0)
	Female	39 (44.3)	40 (46.0)	16 (55.2)	95 (46.6)	68 (51.9)	59 (45.4)	16 (37.2)	143 (47.0)
Ethnicity, *n* (%)	White/Caucasian	82 (93.2)	84 (96.6)	27 (93.1)	193 (94.6)	125 (95.4)	123 (94.6)	43 (100.0)	291 (95.7)
	Arabic/North African	2 (2.3)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.7)
	East/South East Asian	1 (1.1)	1 (1.1)	1 (3.4)	3 (1.5)	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.7)
Care type at enrolment, *n* (%)	At least one sibling at home	21 (23.9)	18 (20.7)	10 (34.5)	49 (24.0)	53 (40.5)	48 (36.9)	13 (30.2)	114 (37.5)
	Attending day care centre	36 (40.9)	37 (42.5)	13 (44.8)	86 (42.2)	62 (47.3)	70 (53.8)	24 (55.8)	156 (51.3)
	Attending a childminder	12 (13.6)	21 (24.1)	8 (27.6)	41 (20.1)	13 (9.9)	17 (13.1)	4 (9.3)	34 (11.2)
	At least once a week contact	59 (67.0)	56 (64.4)	19 (65.5)	134 (65.7)	99 (75.6)	97 (74.6)	32 (74.4)	228 (75.0)

Two-dose, participants having received two doses of measles-mumps-rubella-varicella vaccine; one-dose, participants having received one dose of measles-mumps-rubella vaccine and one dose of varicella vaccine; control, participants having received two doses of measles-mumps-rubella vaccine; total, number of all participants included in all three vaccination groups (two-dose, one-dose and control) per country; *n (%)*, number and percentage of participants belonging to a given category.

Abbreviations: *N*, number of participants included in each group; SD, standard deviation.

*Data for the control group have been published previously.[17]

TABLE 2 Number of study participants with a confirmed varicella case and vaccine efficacy between the second vaccination and the end of the study (according-to-protocol efficacy cohort in Phases A+B)

	Norway			Sweden		
	Number of participants *n/N* (%)	Incidence rate per 100 person-years (95% CI)	Vaccine efficacy % (95% CI)	Number of participants *n/N* (%)	Incidence rate per 100 person-years (95% CI)	Vaccine efficacy % (95% CI)
Two-dose	7/74 (9.5)	1.2 (0.5–2.4)	92.1 (81.1–96.7)	12/120 (10.0)	1.2 (0.7–2.0)	92.6 (85.5–96.3)
One-dose	23/76 (30.3)	4.1 (2.7–6.2)	72.3 (49.0–85.0)	56/116 (48.3)	7.6 (5.9–9.9)	58.0 (34.6–73.0)
Control*	19/25 (76.0)	16.4 (10.4–25.6)	NA	31/39 (79.5)	20.9 (14.7–29.7)	NA

Note: Two-dose, participants having received two doses of measles-mumps-rubella-varicella vaccine; one-dose, participants having received one dose of measles-mumps-rubella vaccine and one dose of varicella vaccine; control, participants having received two doses of measles-mumps-rubella vaccine.

Abbreviations: 95% CI, 95% confidence interval; *N*, number of participants included in each group; *n*, number of participants having reported at least one event of varicella disease; NA, not applicable.

*Data for the control group have been published previously.[17]

4 | DISCUSSION

Two varicella vaccine doses provided at least 92.1% efficacy in both Norwegian and Swedish children, compared to 72.3% in Norway and 58.0% in Sweden for one dose. These results are in line with overall data from the European study, where the vaccine efficacy reported in the 10-year follow-up of children was 95.4% with two varicella vaccine doses and 67.2% with one dose.[15] Similar results were reported in previous varicella vaccine efficacy studies. Efficacy against all varicella ranged from 55% to 87% for one dose of monovalent or tetravalent varicella vaccine versus 84% to 98% for two doses.[14]

Although both vaccination schedules were efficacious in preventing varicella in Norway and Sweden, the estimated 10-year efficacy of the two-dose schedule was higher compared to the one-dose schedule. These results suggest that the two-dose varicella vaccine schedule provides optimum long-term protection for the prevention of all varicella as previously reported.[18] The improved protection conferred by the two-dose varicella vaccination schedule was previously reported in a post-marketing meta-analysis of 42 studies assessing currently licenced monovalent and tetravalent varicella vaccines. In this meta-analysis, a pooled two-dose vaccine effectiveness was estimated at 92% vs. 81% for one dose.[19] Similar results were reported in studies focussing on breakthrough varicella cases. In the first two and a half years after introduction of the second dose, the odds of developing varicella for children who received two varicella vaccine doses were lower than for those who received one dose.[20,21]

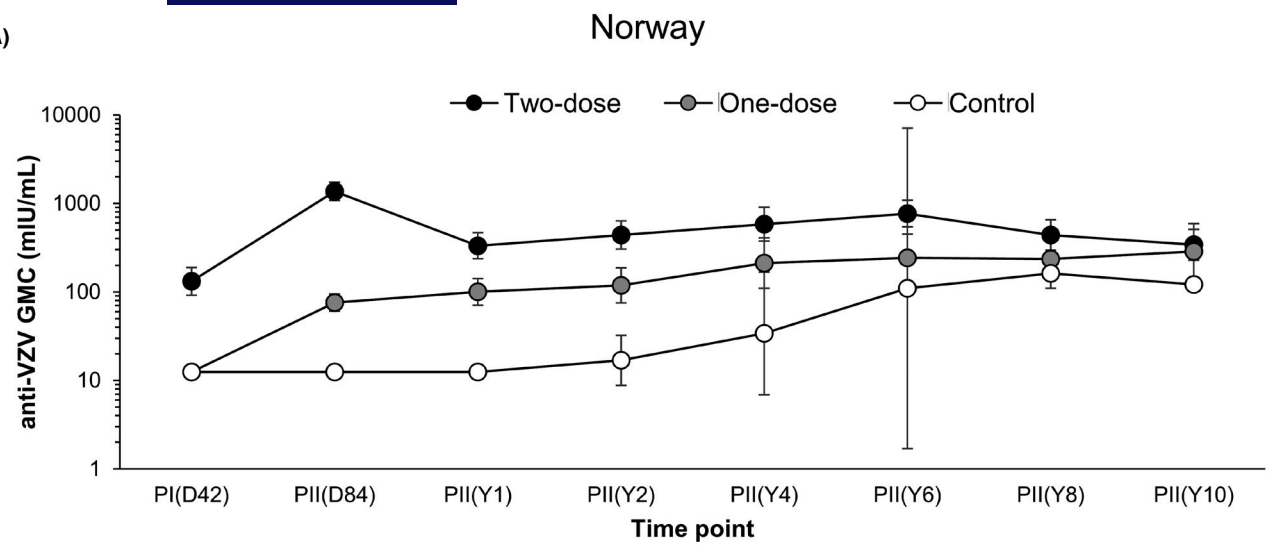
The European-level results of this study showed a higher efficacy against moderate or severe compared to all varicella: 99.1% vs. 95.4% for two doses and 89.5% vs. 67.2% for one dose.[15] Accordingly, even though not directly assessed in our sub-study, a one-dose schedule is also expected to offer a high degree of protection against severe varicella in Norway and Sweden.

Immunogenicity results followed similar trends to the efficacy results. Both in the one-dose and in the two-dose groups, VZV seropositivity rates were at least 90% in Norway and at least 83% in Sweden after the second vaccination and remained high throughout the study. In contrast, seropositivity rates in Norwegian and Swedish children were lower than those observed in the overall study: at least 96% for the two-dose and at least 92% in the one-dose group.[15] Both in Norway and Sweden, anti-VZV antibody concentrations on day 84 were substantially higher in the two-dose compared to the one-dose groups. However, differences in concentrations observed between the groups gradually decreased towards the end of the study. In addition, there was a trend for anti-VZV antibody geometric mean concentration increase over time for the one-dose and control groups. This could be linked to underreporting of varicella cases or subclinical forms of the disease. It could also be linked to a natural boosting effect resulting from exposure of Norwegian and Swedish children to VZV after the start of the study. Overall immunogenicity results of the European study showed similar geometric mean concentration profiles to those presented here.[15] Immune responses against measles, mumps and rubella viruses remained high across the three study groups in both countries throughout the study.

Fever was previously reported to occur more frequently after vaccination with MMRV compared to MMR.[22] However, this trend was not systematically observed in this study. No safety concerns were highlighted during the follow-up period in either the Norwegian or Swedish study populations. These findings support the acceptable safety profiles of the study vaccines previously highlighted by the overall results of this European study.[15]

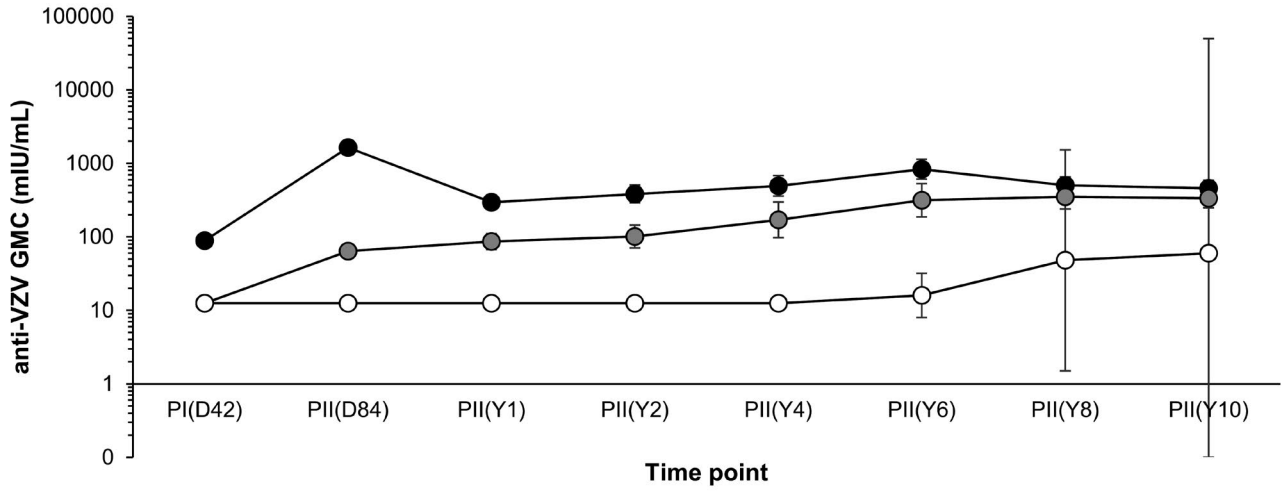
Epidemiological factors are likely to increase the risk of exposure to VZV in Norway and Sweden. These include the relatively high attendance to day care and the higher average number of children per household in these countries compared to the rest of Europe.[23–25] Increased incidence of varicella has been previously reported in children attending day care.[26,27] In our study, more than 40% of children attended day care centres in Norway and Sweden versus 23%–25% in other European countries.[15] This is reflected in the higher incidence rates of confirmed varicella observed in the control groups in Norway and Sweden compared to the overall results of this European study.[15,17] While the incidence rates of varicella in the control groups were 16.4 and 20.9/100 person-years in Norway and Sweden, respectively, this was 10.6/100 person-years

(A)



Seropositivity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Two-dose	15 (100)	64 (100)	55 (98.2)	48 (100)	39 (100)	43 (100)	25 (100)	26 (100)
One-dose	0 (0.0)	62 (92.5)	58 (96.7)	43 (91.5)	29 (93.5)	26 (92.9)	18 (90.0)	21 (91.3)
Control	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	2 (25.0)	2 (50.0)	1 (100)	1 (100)

(B)



Seropositivity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Two-dose	64 (91.4)	115 (100)	103 (100)	97 (100.0)	77 (98.7)	78 (98.7)	79 (97.5)	80 (97.6)
One-dose	0 (0.0)	95 (89.6)	84 (89.4)	67 (87.0)	44 (83.0)	42 (91.3)	46 (97.9)	47 (100)
Control	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (50.0)	1 (33.3)

FIGURE 3 Anti-VZV antibody geometric mean concentrations and seropositivity rates (percentages of participants with anti-VZV concentrations ≥25 mIU/mL) for initially seronegative participants with censored post-infection data (adapted according-to-protocol cohort for persistence in Phases A+B, subset for PI(D42)). (A) Norwegian cohort, (B) Swedish cohort. Two-dose, participants having received two doses of measles-mumps-rubella-varicella vaccine; one-dose, participants having received one dose of measles-mumps-rubella vaccine and one dose of varicella vaccine; control, participants having received two doses of measles-mumps-rubella vaccine; anti-VZV, antibodies specific for varicella-zoster virus; GMC, geometric mean concentration; mIU/mL, milli-international units per mL; PI(D42), study visit 42 days after the first vaccine dose; PII(D84), study visit after the second vaccine dose; PII(Y1)–PII(Y10), study visits at 1, 2, 4, 6, 8 and 10 years after the second vaccine dose; *n* (%), number and percentage of seropositive participants. The error bars represent 95% confidence intervals

overall. However, efficacy results obtained for the monovalent and tetravalent varicella vaccines in Norway and Sweden seemed comparable and similar to vaccine efficacy reported overall in this European study.[15] A seasonal component to varicella incidence has been previously reported.[28] However, this is unlikely to account for differences in incidence rates observed in Norway and Sweden compared to other European countries included in this study. Some of these, such as Lithuania, Russia and Poland, also have cold winters and marked seasons. Lastly, the reduction in contact between children during the summer holidays results in a reduced transmission of VZV.[26] However, it is also unlikely that correlations between VZV transmission and the school calendar account for these differences.

The main strength of this study is the robust study design. This includes the 10-year follow-up, the large number of participants and the confirmation of varicella cases by an independent data monitoring committee. Also, participating children were vaccinated with two different varicella vaccines or a control vaccine, according to different vaccination schedules. Varicella vaccine schedules included either one dose or two doses. In addition, varicella is an endemic disease in all countries involved in this European study, including Norway and Sweden. Vaccine efficacy estimates will therefore factor in potential biases associated to real-world settings, such as natural boosting phenomena. Moreover, as mentioned above, both monovalent and tetravalent varicella vaccines used in this study contain the same Oka VZV strain. The results therefore enable comparison between the vaccines that contain the Oka strain when used according to a one-dose or two-dose regimen.

The main limitation of the analyses presented here is their descriptive nature. Although results may provide insights into the benefits of varicella vaccination, this 10-country European study was not powered to statistically conclude on vaccine efficacy estimates for each participating country. Moreover, the low number of study participants from the Nordic compared to other participating countries did not allow for a meaningful analysis of efficacy according to severity. In our sub-study, efficacy was only evaluated in the according-to-protocol cohort. However, in the entire study population, a sensitivity analysis performed on the total vaccinated cohort showed similar vaccine efficacy to that estimated in the according-to-protocol cohort for efficacy.[15] The gradual implementation of universal varicella vaccination prior to or during the course of the European study, such as in Greece and Italy, may have altered levels of circulating VZV and the natural boosting effect. Consequently, efficacy estimates for these countries might have been impacted indirectly. Also, the high levels of circulating varicella in Norway and Sweden might have had a natural boosting effect. This might have impacted anti-VZV antibody concentrations and seropositivity rates in the two-dose and one-dose groups in these countries. However, as the study design is not appropriate to evaluate this effect, its influence on the results of the present study remains unclear. In addition, the number of participants from the control groups included in the immunogenicity assessments was small, which is an inherent limitation of this sub-group analysis.

The results presented here further highlight the potential of implementing universal varicella vaccination. A monovalent vaccine was first introduced in the routine childhood immunisation programme in the USA in 1995. Other countries, including several European countries, also introduced universal varicella vaccination programmes, all resulting in marked reductions in varicella incidence and hospitalisation rates.[11,29,30] Since then, two-dose varicella vaccination schedules also demonstrated efficacy against breakthrough cases of varicella. In light of this, implementation of a two-dose universal varicella vaccination programme is now recommended by the World Health Organization.[3] It has been estimated that in the absence of universal varicella vaccination, the burden of varicella would be considerable. More than 5 million varicella cases would occur annually in Europe. This would result in the need for primary care for 3.0–3.9 million of affected patients, 18,200–23,500 hospitalisations and 80 varicella-related deaths.[6]

5 | CONCLUSION

A marked reduction in the incidence of varicella was observed following vaccination with two doses of MMRV or one dose of monovalent varicella vaccine over a 10-year post-vaccination period in Norwegian and Swedish children. In addition to high efficacy, both vaccination schedules provided a high level of immunogenicity persistence and had acceptable safety profiles. Along with overall results of this European study, data presented here provide valuable information about the benefits of varicella vaccines, in particular when administered following a two-dose schedule. These data may also support decisions to implement universal varicella vaccination in European countries, such as Norway and Sweden.

6 | Trademark statement

Priorix, *Priorix-Tetra* and *Varilrix* are owned by or licenced to the GSK group of companies. *Varivax* and *ProQuad* are trademarks of Merck Sharp & Dohme Corp.

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CONFLICT OF INTERESTS

GC, MAH and MP are employees of the GSK group of companies, and GC and MAH are also shareholders. SAS has received personal fees from the GSK group of companies in relation to other studies. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The protocol of this study is available at gsk-studyregister.com (ID 100388). Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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