The Effectiveness of Varicella Vaccination in Children in Germany

A Case-control Study

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Background: Effectiveness of 1 dose of varicella vaccination was estimated to be 85–88% against clinical varicella of any severity in case-control studies in non-European countries, but lower effectiveness has been demonstrated in outbreaks.

Methods: A prospective, age- and practice-matched case-control study was conducted in Germany to assess the effectiveness of 1 dose of OKA/GSK varicella vaccine (derived from the OKA strain, a Japanese clinical isolate) and of any varicella vaccine (including OKA/GSK, OKA/Merck and MMR-OKA/GSK) against polymerase chain reaction (PCR)-confirmed varicella under conditions of routine use.

Results: The cohort included 432 PCR-confirmed cases and 432 matched controls (1–7 years old). Varicella vaccination was reported for 13.2% (57/432) of cases and 45.1% (195/432) of controls. Median time since vaccination was 28 and 25 months, respectively. Vaccinated cases experienced milder disease ($P < 0.0001$) and shorter duration of disease ($P = 0.004$) compared with unvaccinated cases. After adjusting for gender and school/day-care attendance, vaccine effectiveness of 1 dose of OKA/GSK against PCR-confirmed varicella of any severity was 71.5% (95% confidence interval [CI]: 49.1–84.0) and 94.7% (95% CI: 77.8–98.7) against PCR-confirmed moderate or severe varicella. Adjusted effectiveness for any varicella vaccine was 86.4% (95% CI: 77.3–91.8) against any severity and 97.7% (95% CI: 90.5–99.4) against moderate or severe varicella.

Conclusions: One dose of varicella vaccine provided high protection against moderate and severe varicella disease for a period of up to 5 years after vaccination. However, further effectiveness data are needed to assess long-term protection.

Key Words: varicella, vaccination, Germany, children

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Varicella, or chickenpox, is caused by the varicella-zoster virus (VZV), a highly communicable herpes virus with a secondary attack rate of up to 90% among susceptible household contacts. In unvaccinated populations, approximately 90% of varicella infections occur in children between 1 and 14 years of age.[1,2] Immunity after varicella disease is generally long lasting, but the virus remains latent in human nerve tissue and can reactivate, resulting in herpes zoster, particularly in individuals older than 50 years.[3]

Before the introduction of routine varicella vaccination in Germany, 62.5% of children had already been infected by varicella by the age of 5 years and 94.2% by 10–11 years of age.[4] There were an estimated 14.1 varicella hospitalizations per 100,000 children in Germany.[5] This was in the mid-range observed in other studies from Europe and the United States, with 0.9–29.4 hospitalizations per 100,000 children.[5] The most common varicella-associated complications in hospitalized children in Germany were neurologic, skin infection and gastrointestinal tract complications, with permanent sequelae reported in 1.7%.[5,6] The estimated annual varicella-associated mortality rate before implementation of routine varicella vaccination was 0.4/1,000,000 children <17 years of age in Germany[7] and 0.65/1,000,000 children <20 years of age in the United States.[8]

Although varicella vaccines are licensed in many countries, routine childhood varicella vaccination is only implemented in Australia, Canada, Costa Rica, Ecuador, Germany, Greece, Italy (7 of 21 regions), Israel, Latvia, Luxembourg, Oman, Panama, Qatar, Saudi Arabia, South Korea, Spain (2 of 17 regions), Taiwan, the United Arab Emirates, Uruguay and the United States.[9–15] As the first country in Europe, Germany introduced routine varicella vaccination in July 2004, with 1 dose for all infants and children between 11 and 14 months of age.[16] In 2006, vaccination coverage for 1 dose of varicella vaccine among children 18–36 months was 38% in the area of Munich, increasing to 51% in 2007, to 53% in 2008 and 2009 and to 66% in 2010[17] (also Streng et al, unpublished data). Extrapolated nationwide coverage for Germany among 24-month-old children was estimated as 38% in 2006, 63% in 2007 and 78% in 2008.[18] In 2009, a 2-dose schedule was recommended for all ages, with both doses applied in the second year of life for all licensed varicella vaccines.[19]

The monovalent OKA/Merck vaccine (Varivax®; Merck, Whitehouse Station, NJ) was licensed in the United States in 1995, resulting in impressive decline of varicella incidence, hospitalizations and mortality after implementation of the 1-dose vaccination

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program.[8,20–22] In case-control studies, OKA/Merck showed a 1-dose vaccine effectiveness of 85% [95% confidence interval (CI): 78–90][23] and 87% (95% CI: 81–91)[24] against varicella of any severity and of 97% (95% CI: 93–99) against moderate or severe infection,[23] whereas the effectiveness of 2 doses was 98% (95% CI: 84–100) against varicella of any severity.[25] Nevertheless, even in highly vaccinated populations in the United States, varicella outbreaks occurred frequently.[26,27] Case-control studies from Israel and China on OKA/GSK (Varilrix®; GlaxoSmithKline, Wavre, Belgium) estimated the effectiveness of 88% (95% CI: 77–94) against clinical varicella of any severity and 100% against moderate or severe illness,[28] and 86% (95% CI: 73–93) against clinical varicella, respectively.[29] None of the previously published OKA/GSK case-control studies used laboratory-confirmed cases of varicella. Furthermore, no effectiveness data from case-control studies on varicella vaccines are available from Europe thus far. The objective of the present case-control study was to assess the effectiveness of 1 dose of OKA/GSK and of any marketed varicella vaccines (OKA/GSK, OKA/Merck and MMR-OKA/GSK) against varicella under conditions of routine use in pediatric practices in Germany.

MATERIALS AND METHODS

Study Setting and Objectives

From February 2008 to October 2010, a prospective, age- and practice-matched case-control study was conducted in 35 pediatric practices caring for approximately one quarter of the pediatric population from the Munich (Bavaria) area and its adjacent districts. In this area, there was an average annual pediatric population of approximately 238,000 children <17 years of age and 78,000 children <5 years of age during the years 2005 to 2010.[30] The primary objectives of the study were to assess the effectiveness of 1 dose of OKA/GSK against polymerase chain reaction (PCR)-confirmed varicella of any severity. The effectiveness of 1 dose of any available varicella vaccines, including OKA/GSK, OKA/Merck and MMR-OKA/GSK, was also studied, as well as the effectiveness against clinical varicella (ie, irrespective of laboratory confirmation).

Sample Size for Vaccine Effectiveness for 1 Dose of OKA/GSK

Sample size was estimated for the main objective of the study, that is, to measure vaccine effectiveness for 1 dose of OKA/GSK vaccine, under the following assumptions: vaccination coverage of 25%, vaccine effectiveness of 80%, OKA/GSK representing 60% of varicella vaccine used and 15% exclusion of PCR-confirmed cases due to absence of age-matched controls or to vaccination within a 28-day window. Under these assumptions, to provide 80% power that the lower limit of the 95% CI of vaccine effectiveness would be >50%, enrollment was planned for at least 420 PCR-confirmed varicella cases and an equal number of matched controls.

Inclusion and Exclusion Criteria

Children at least 1 year of age, born on or after July 1, 2003, who had their residence in Germany, at least 1 previous well-child visit to the practice, and for whom written informed consent was provided, were eligible to participate as cases if they had suspected clinical varicella disease at the time of study entry. Children matched by age and pediatric practice, fulfilling the same criteria as cases but without history or present clinical diagnosis of varicella, were eligible to be included as controls. Children were excluded from participating as a case or control if they had any history of hypersensitivity to any component of the varicella vaccines, a congenital or acquired immunodeficiency, were receiving treatment with immunosuppressive therapy, had a previous history of varicella by physician records or parental report or had a lack of documented vaccination history.

Study Recruitment and Procedures

For all potential varicella cases, the child's pediatrician informed the study physician. After the parents or guardians provided informed consent, the study physician visited the child at home, preferably within 5 days of varicella onset. Up to 3 samples were obtained per child for PCR confirmation of varicella. Clinical information including the date of onset of rash, number of lesions, type of lesions, presence of fever or other symptoms and an assessment of severity of disease were recorded. The study physician was blinded to the child's varicella vaccination status until clinical assessment was completed. At the end of the home visit, the vaccination status was documented according to the child's vaccination card. The child's pediatrician collected data from medical records including demographic data, the child's medical history and vaccination status [for varicella and for measles-mumps-rubella (MMR)] as documented in the patient chart. Follow-up data on disease outcome and complications were obtained by phone call with the parent or guardian 2–4 weeks after study visit.

One age- and practice-matched control child per case child was recruited after a standardized procedure by identifying the child closest in date of birth to the case child from the practice records. In case this child did not fulfill the inclusion criteria for controls, or if the parent/guardian could not be contacted within an interval of 2 days with at least 3 attempts, the child with the next closest date of birth was identified. Once a control was eligible and written consent had been provided, the child's medical history and vaccination status were obtained from the practice medical records. The pediatrician verified these data and supplemented demographic data by calling the parents or guardians by phone.

Cases were classified as vaccinated varicella cases if they had received OKA/GSK, OKA/Merck or the combined MMR-OKA/GSK vaccine at least 28 days before varicella onset. Controls were classified as vaccinated if they had received OKA/GSK, OKA/Merck or MMR-OKA/GSK vaccine at least 28 days before varicella onset in the matched case. Severity assessment of varicella disease was based on a clinical scale as used in a previous study.[23] A severity score of ≤7 was classified as mild, 8–15 was classified as moderate, and a score of ≥16 was classified as severe varicella disease.

The study protocol, any amendments, the informed consent and other information that required preapproval were reviewed and approved by regional and investigational center Institutional Ethics Committee or Institutional Review Board, Ethical Committee of the Medical Faculty of the University of Munich and the Ethical Committee of the Bavarian Medical Association.

Laboratory Analysis

Specimens from skin lesions were collected by unroofing a fluid-filled vesicle, scabs or crusts with a sterile needle. If vesicular fluid was not sufficient or lesions were dry, samples were collected by gently rubbing the base of the lesions. Specimens were stored and transported at −20°C and, after shipment to the central laboratory (GlaxoSmithKline Vaccines), varicella infection was confirmed by the detection of VZV DNA through quantitative PCR (qPCR). This qPCR VZV technique was used to amplify a VZV open reading frame 62 region.[31] Samples were considered positive for VZV DNA if the qPCR signal exceeded the copy number limit of detection determined by VZV DNA standard curve. To confirm DNA integrity for samples that were VZV DNA negative, qPCR for the housekeeping gene, actin, was

performed. If a sample was VZV DNA and actin negative, it was considered an invalid (indeterminate) result. Primer and probe sets specific for VZV (forward: 5′ gtggccctcgagaggtgg 3′, reverse: 5′ caaaggtgcgcgacgatg 3′, probe: 5′ FAM-ccgggccgtgtttgcatcg-BHQ 3′) and actin (forward: 5′ ctggaacggtgaaggtgaca 3′, reverse: 5′ ggccacattgtgaactttg 3′, probe: 5′ FAM-cagtcggttggagcgagcatccc-EDQ 3′) were used in the following PCR program: uracil DNA glycosylase, activation 50°C/2 minutes, 95°C for 10 minutes followed by 40 cycles of 95°C/15 seconds (denaturation) and 60°C/60 seconds (annealing/extension). In cases with >1 laboratory result per child, at least 1 positive result was considered positive for varicella. The laboratory personnel analyzing the specimens were not aware of the participant's vaccination status.

Statistical Analysis

Statistical analyses were conducted using the "according to protocol" (ATP)-confirmed cases cohort and their matched controls (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B579). Analysis of vaccine effectiveness for clinical varicella was performed on the ATP-enrolled cases and ATP-matched control cohort, including additional varicella cases with negative or indeterminate PCR results and their matched controls. Fisher's exact test was used for statistical comparison of categorical variables. Wilcoxon rank-sum test was used to assess statistical significance between groups for continuous variables. All *P* values were 2-sided, and results were considered statistically significant if the 2-tailed *P* value was <0.05.

Multiple logistic regression was used to model the relationship between the probability of having varicella and varicella vaccination, adjusting for possible confounders. Model building was performed through a forward selection strategy combined with prior knowledge of possible confounders.[23,29] Selection started from the basic model (varicella vaccination) and, based on the literature, also included gender and school or day-care attendance. Other variables [treatment with steroids or other immunosuppressants, presence of asthma, country of birth (Germany or other), receipt of varicella vaccine within 28 days of receiving MMR vaccine, preexisting medical conditions, type of health insurance (social/private), total number of well-baby visits and number of sick-child visits over the preceding 12 months] were introduced individually and were retained in the model if they were statistically significant at the $P = 0.05$ level.

Vaccine effectiveness was calculated as 1 minus the matched odds ratio multiplied by 100%. The matched odds ratio for vaccination was calculated using conditional logistic regression, with associated *P* values and 95% CIs. To estimate the effect of time since vaccination, a dummy variable was created for each possible year during which vaccinated children could have developed the disease. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Recruitment

Between February 2008 and June 2010, 35 pediatric practices reported 908 clinically suspected varicella cases; 81.8% of these potential cases were seen in the practice, 17.4% diagnosed by phone and 0.8% identified otherwise. Ultimately, 480 cases and their matched controls met the criteria for inclusion in the ATP-enrolled cohort (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B579). Ninety percent (432/480) of cases had positive PCR results and 10% (48/480) had negative or indeterminate PCR results, resulting in an ATP-confirmed cohort of 432 cases and 432 matched controls.

General Characteristics of Cases and Controls

General characteristics of the 432 cases and their matched controls are shown in Table 1. Demographic characteristics of cases and controls were similar, except that cases had attended day care for a median of 17 days during the month before the onset of varicella compared with 20 days in the controls ($P < 0.0001$; Table 1).

Regarding the vaccination status of the 432 varicella cases, 375 (86.8%) were not vaccinated against varicella, 55 (12.7%) had received 1 dose of any varicella vaccine and 2 (0.5%) had received 2 doses of any varicella vaccine (Table 1). Of the 55 cases vaccinated with 1 dose, 35 (63.6%) had received OKA/GSK and 19 (34.5%) either OKA/Merck [15 (27.3%)] or MMR-OKA/GSK [4 (7.3%)]; vaccine type was unknown in 1 case (1.8%; Table 1). The mean age at the time of the first dose of any varicella vaccine was 1.1 years (standard deviation 0.7) among vaccinated confirmed cases. The median time since vaccination was 28 months (range: 5–57; interquartile range: 20; Q1: 18; Q3: 38). A total of 343 (79.4%) cases had received at least 1 dose of an MMR vaccine (with any available MMR vaccine or MMR-OKA/GSK). Of these, 337 (98.3%) received solely MMR vaccine (80.5% received 2 doses, 17.8% received 1 dose).

A higher proportion of controls had received varicella vaccination compared with cases (45.1% versus 13.2%, $P < 0.0001$; Table 1). Among the controls, 237 (54.9%) were unvaccinated against varicella, 153 (35.4%) had received 1 dose of any varicella vaccine and 42 (9.7%) had received 2 doses of any varicella vaccine. Of the 153 controls vaccinated with 1 dose, 63 (41.2%) had received OKA/GSK and 87 (56.9%) either OKA/Merck [73 (47.7%)] or MMR-OKA/GSK [14 (9.2%)]; vaccine type was unknown for 3 controls (2.0%; Table 1). The mean age at the time of the first dose of any varicella vaccine was 1.3 years (standard deviation 1.1) among vaccinated controls. The median time since vaccination was 25 months (range: 1–54; interquartile range: 22). The proportion of children receiving any MMR vaccination (any MMR vaccine or MMR-OKA/GSK) was not different among cases and controls (Table 1).

Comparison of Vaccinated and Unvaccinated Cases

Onset of varicella, both in the 57 vaccinated and 375 unvaccinated confirmed cases, varied by season, first usually with an increase in November and peaking in spring (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/B580). A comparison of the vaccinated and unvaccinated cases is given in Table 2. A greater proportion of unvaccinated versus vaccinated cases experienced fever after the onset of varicella (61.0% versus 35.7%). Unvaccinated cases also had a higher median severity of disease score (8 versus 5, $P < 0.0001$) and more lesions compared with vaccinated cases (12.3% of unvaccinated cases had 1–50 lesions versus 61.4% of vaccinated cases, $P < 0.0001$). Median duration of varicella was 1 day longer in unvaccinated compared with vaccinated cases (9 versus 8 days, $P = 0.0041$).

Systemic signs after the onset of varicella were reported for 1 of the 57 vaccinated cases (1.8%) and for 37 of the 375 unvaccinated cases (9.9%). The majority of systemic signs were pain in the back or abdomen (in 1 vaccinated case and in 35 unvaccinated cases); 1 unvaccinated case presented with interstitial pneumonia. Overall, 43 vaccinated cases (75.4%) and 353 of unvaccinated cases (94.1%) reported medical treatment during the illness. The most frequently reported medication was antipyretic, reported for 3 vaccinated cases and 48 unvaccinated cases. Eleven (19.3%) of 57 vaccinated case patients needed an additional physician consultation for varicella treatment. In comparison, 64 (17.1%) of 375 unvaccinated case patients needed a medical visit; of these, 61 needed physician

TABLE 1. Comparison of Demographics and Vaccination History of Confirmed Varicella Cases and Matched Controls (ATP Cohort for Confirmed Cases and Matched Controls)

	Cases (N = 432)	Controls (N = 432)	*P*
Age, yr			
Median	3.0	4.0	0.3148
Range	1–6	1–7	
Male gender	217 (50.2%)	220 (50.9%)	0.8918
Median number of previous well-child visits	8.0	8.0	0.1517
Preexisting medical condition	78 (18.1%)	100 (23.1%)	0.0771
Day-care attendance	363 (84.0%)	351 (81.3%)	0.3232
Median number of days in day care (per month)	17.0	20.0	<0.0001
School attendance	7 (1.6%)	6 (1.4%)	1.000
Health insurance			0.3861
Statutory	295 (68.3%)	282 (65.3%)	
Private	137 (31.7%)	150 (34.7%)	
Received any MMR vaccination (MMR or MMR vaccine)	343 (79.4%)	357 (82.6%)	0.2594
Received any varicella vaccination	57 (13.2%)	195 (45.1%)	<0.0001
Among vaccinated cases/controls only	(n = 57)	(n = 195)	
Number of doses of varicella vaccine administered more than 28 days before onset/focal time*			0.0011
1	55 (96.5%)	153 (78.5%)	
2	2 (3.5%)	42 (21.5%)	
Age of first vaccination is <12 mo	8 (14.0%)	38 (19.5%)	0.4372
Age of first vaccination is <15 mo	41 (71.9%)	114 (58.5%)	0.0882
Type of varicella vaccine for doses >28 days before onset/focal time			<0.0001
OKA/GSK (1 dose)	35 (61.4%)	63 (32.3%)	
OKA/GSK (2 doses)	0 (0.0%)	6 (3.1%)	
Other than OKA/GSK (1 dose)†	19 (33.3%)	87 (44.6%)	
Other than OKA/GSK (2 doses)†	2 (3.5%)	25 (12.8%)	
1 dose of OKA/GSK and 1 dose of other (2 doses)†	0 (0.0%)	11 (5.6%)	
Unknown (1 dose)	1 (1.8%)	3 (1.5%)	

*Missing data: varicella vaccination dose number was missing for 1 control participant.
†"Other than OKA/GSK" includes OKA/Merck and MMR-OKA/GSK.

consultations and 3 emergency room visits; 1 child was hospitalized due to pneumonia. None of the vaccinated cases but 24 (6.4%) of the unvaccinated cases reported sequelae of permanent scars.

Multiple Logistic Regression Analyses

All vaccine effectiveness models were adjusted for gender and school or day-care attendance; all other variables were excluded from the model during the modeling process as they were not statistically significant (at $P = 0.05$ level). Unadjusted and adjusted values for vaccine effectiveness were very similar for all estimates (Table 3). The primary outcomes were an adjusted effectiveness of 1 dose against PCR-confirmed varicella of any severity of 71.5% (95% CI: 49.1–84.0) for OKA/GSK and 86.4% (95% CI: 77.3–91.8) for any varicella vaccine, including OKA/GSK (Table 3). The adjusted effectiveness against PCR-confirmed moderate or severe varicella was 94.7% (95% CI: 77.8–98.7) for OKA/GSK and 97.7% (95% CI: 90.5–99.4) for any varicella vaccine (including OKA/GSK). The effectiveness of 1 dose of any varicella vaccine (including OKA/GSK) against clinical varicella of any severity (including 48 cases with negative or indeterminate PCR results) was 81.1% (95% CI: 71.0–87.7; unadjusted) and 81.2% (95% CI: 71.2–87.8; adjusted). The effectiveness of 2 doses of any varicella vaccine (including OKA/GSK) against PCR-confirmed varicella of any severity was high in both the unadjusted (94.3%, 95% CI: 76.2–98.6) and the adjusted (94.3%, 95% CI: 76.4–98.6) model. Age at vaccination (<15 months or ≥15 months) did not have an effect on vaccine effectiveness, neither as a main effect nor in interaction with time since vaccination. The effectiveness of 1 dose of OKA/GSK or any varicella vaccine against PCR-confirmed severe varicella could not be evaluated due to the low number of severe cases (no vaccinated and only 3 unvaccinated severe cases).

The effectiveness of 1 dose of OKA/GSK was 84.6% (95% CI: 31.8–96.5) up to 1 year after vaccination, 41.9% (95% CI: −52.6 to 77.9) during the second year after vaccination and 75.9% (95% CI: −20.8 to 95.2) 4–5 years after vaccination. With any varicella vaccine, it was 94.5% (95% CI: 76.9–98.7) up to 1 year after vaccination, 81.5% (95% 56.8–92.1) in the second year after vaccination and 73.2% (95% CI: 9.1–92.1) 4–5 years after vaccination (Fig. 1). The difference in effectiveness over the entire period was not statistically significant, with a global *P* value for equality test between all years of 0.543 for OKA/GSK and 0.235 for any varicella vaccine (including OKA/GSK).

DISCUSSION

Principal Findings

This is the first case-control epidemiological study of the effectiveness of 1-dose varicella vaccination under conditions of routine use in Europe. Children with varicella in this study were between 1 and 6 years of age; 87% were unvaccinated. Vaccinated cases had received the vaccine at a median time of 28 months before the onset of disease. As seen previously,[20] breakthrough cases in varicella-vaccinated children had a significantly milder clinical course when compared with cases among unvaccinated children, with fewer lesions and a shorter duration of disease. The adjusted effectiveness of 1 dose of OKA/GSK against PCR-confirmed varicella disease of any severity was 71.5% (95% CI: 49.1–84.0), and for all investigated varicella vaccines (including OKA/GSK, OKA/Merck and MMR-OKA/GSK), the effectiveness was 86.4% (95% CI: 77.3–91.8). With regard to moderate or severe PCR-confirmed varicella, the effectiveness of OKA/GSK was 94.7% (95% CI: 77.8–98.7), similar to the 97.7% (95% CI: 90.5–99.4) effectiveness for any varicella vaccine.

TABLE 2. Comparison of Vaccinated and Unvaccinated Confirmed Varicella Cases (ATP Cohort for Confirmed Cases)

	Vaccinated (N = 57)	Unvaccinated (N = 375)	*P*
Age, yr			
Median	3.0	3.0	0.7298
Range	1–6	1–6	
Male gender	34 (59.6%)	183 (48.8%)	0.1550
Day-care attendance	54 (94.7%)	309 (82.4%)	0.0184
Median number of days in day care	17.0	17.0	0.9684
Preexisting medical condition*	9 (15.8%)	69 (18.4%)	0.7147
Exposure to varicella or zoster in previous 3 wk*	49 (90.7%)	308 (94.8%)	0.2204
Fever after the onset of varicella*	20 (35.7%)	225 (61.0%)	0.0005
Severity of disease*			
Median severity score	5	8	<0.0001
Mild	49 (87.5%)	113 (31.7%)	<0.0001
Moderate	7 (12.5%)	235 (66.0%)	
Severe	0 (0.0%)	8 (2.2%)	
Estimated number of lesions			<0.0001
1–50	35 (61.4%)	46 (12.3%)	
51–100	17 (29.8%)	112 (29.9%)	
101–500	5 (8.8%)	187 (49.9%)	
>500	0 (0.0%)	30 (8.0%)	
Needed second medical visit	11 (19.3%)	64 (17.1%)	0.7076
Varicella disease complications	0 (0.0%)	6 (1.6%)	1.000
Outcome			0.0522
Recovered	57 (100.0%)	342 (91.2%)	
Recovered with sequelae	0 (0.0%)	26 (6.9%)	
Recovering	0 (0.0%)	7 (1.9%)	
Duration—median number of days	8	9	0.0041

*Missing data: preexisting condition listed "unknown" for 1 unvaccinated confirmed case, severity score missing for 1 vaccinated case and 19 unvaccinated cases, varicella exposure missing for 3 vaccinated cases and 50 unvaccinated cases, fever after onset unknown for 1 vaccinated case and 6 unvaccinated cases. Proportions were calculated excluding missing data.

Exploratory analyses of vaccine effectiveness over time were not powered to measure a potential decrease in effectiveness according to time since vaccination. The difference in effectiveness by year was not statistically significant. The apparent decrease in vaccine effectiveness according to time since vaccination after 1 dose varicella vaccination should be interpreted with caution. Other authors have suggested that this could potentially reflect waning immunity, and/or the age-specific incidence of varicella, which peaks around 4–5 years of age in countries that do not vaccinate routinely, and at an older age if vaccination coverage increases.[27,32] The vaccine effectiveness per year follows the same pattern as reported by Fu et al,[29] with the highest vaccine effectiveness during the first year after vaccination and the lowest in the second year after vaccination. The drop in effectiveness in the second year after vaccination followed by an increase in the following year observed in both studies may be due to the effect of age corresponding to the entry to child-care units or school.[32,33] Frequent outbreaks after vaccination with 1 dose,[26] thought to be mainly due to primary vaccine failure[34] and partly due to waning immunity,[32] resulted in the recommendation of a second dose of varicella vaccine in childhood vaccination programs both in the United States in 2007[35,36] and in Germany in 2009.[19] In the present study, the effectiveness of 2 doses of any varicella vaccine (94.3%, 95% CI: 76.4–98.6) was similar to what was found in a US-based study of 2 doses of OKA/Merck (98.3%, 95% CI: 83.5–100).[25]

Strengths and Limitations

Strengths of our study were the prospective design with predefined case definitions, including PCR confirmation of cases, and assessment of the clinical status and severity of disease for all enrolled cases by a trained study physician. Due to the restriction to a specific geographic area, the study population was homogenous; in the enrolled cohort, there was no indication of bias.[33,37] Both cases and controls were routine clients of the participating practices with similar frequencies of well- and sick-child visits, and vaccination status according to practice record and vaccination cards of the cases were in good accordance, suggesting that misclassifications

TABLE 3. Varicella Vaccine Effectiveness Results (ATP Cohort for Confirmed Cases and Matched Controls)

	Unadjusted Vaccine Effectiveness (95% CI)	Adjusted* Vaccine Effectiveness (95% CI)
Effectiveness of 1 dose of OKA/GSK against PCR-confirmed varicella (any severity)	70.6% (47.7–83.5)	71.5% (49.1–84.0)†
Effectiveness of 1 dose of any varicella vaccine against PCR-confirmed varicella (any severity)‡	86.1% (76.9–91.7)	86.4% (77.3–91.8)§
Effectiveness of 1 dose of OKA/GSK against PCR-confirmed varicella (moderate or severe)	94.1% (75.5–98.6)	94.7% (77.8–98.7)
Effectiveness of 1 dose of any varicella vaccine against PCR-confirmed varicella (moderate or severe)‡	97.6% (90.1–99.4)	97.7% (90.5–99.4)

*Adjusted for gender and school or day-care attendance.
†Effectiveness in children vaccinated at 15 months or older was not statistically significantly different from those vaccinated before 15 months (71.7% vs. 75.2%, $P = 0.644$).
‡"Any varicella vaccine" includes OKA/GSK, OKA/Merck and MMR-OKA/GSK.
§Effectiveness in children vaccinated at 15 months or older was not statistically significantly different from those vaccinated before 15 months (86.4% vs. 87.0%, $P = 0.822$).

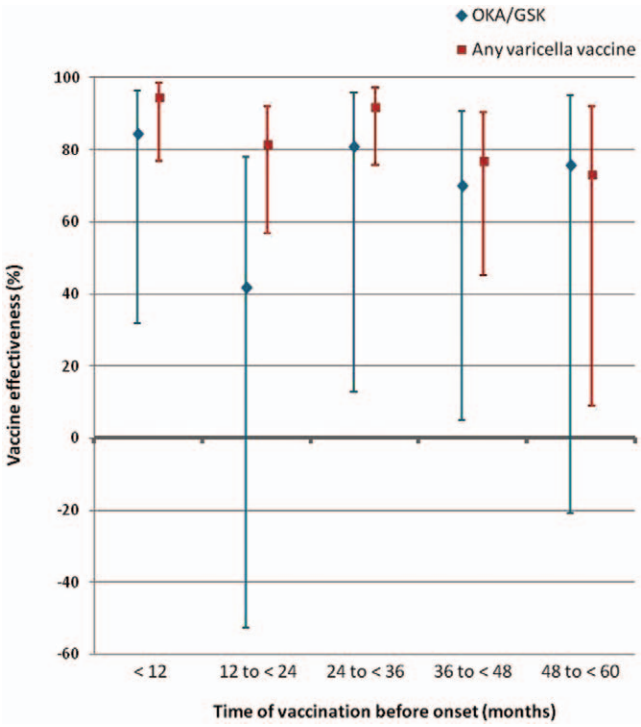

FIGURE 1. Varicella vaccine effectiveness (1 dose) over time against PCR-confirmed varicella of any severity (ATP cohort for confirmed cases and matched controls). Bars represent 95% CIs. Global *P* value for equality test between all years was 0.543 for OKA/GSK and 0.235 for any varicella vaccine (includes OKA/GSK, OKA/Merck, MMR-OKA/GSK).

of vaccination status in controls were minimal. There was also no indication for selection bias related to parents' acceptance of childhood vaccinations[23,37] when we compared the receipt of trivalent MMR vaccination (93% of participants) between cases and controls, based on the assumption that receipt of an MMR vaccination does not influence the likelihood of varicella disease.

The point estimates on vaccine effectiveness for any varicella vaccine were higher than the point estimates for OKA/GSK vaccine during the first 4 years after vaccination. However, this study was not designed or powered to evaluate the difference between vaccines, and therefore, any statistical comparison would not be appropriate. Another limitation of this study is that the investigated population may not be fully representative for other areas of Germany where varicella vaccination coverage might be slightly higher.[18] It has been shown that high levels of vaccination coverage typically lead to high levels of herd protection, as in the United States and Uruguay.[13,38] Herd protection in our study population is estimated to be limited because varicella vaccination coverage among controls, who reflect the general population from which the cases arose, was 47.5%. Frequent exposure to wild-type virus, as in our study, may have resulted in an increased risk of varicella breakthrough disease, especially in children vaccinated with 1 dose and, therefore, in a decreased estimate of vaccine effectiveness. Nevertheless, we could show that even under real-life conditions with low vaccination coverage, varicella vaccines were very effective. It should also be noted that vaccine effectiveness was investigated only up to 5 years after vaccination, and therefore long-term effectiveness could not be assessed. Finally, the small proportion of children who had received more than 1 dose of a varicella vaccine restricted our ability to examine the effect of the 2 doses recommended in Germany since 2009.

Relation to Other Studies

The results of the study are in agreement with previous estimates of vaccine efficacy from prelicensure randomized clinical trials (from 72% to 100% for 1 dose),[39] as well as with vaccine effectiveness results from retrospective data analysis[40] and outbreak investigations,[41–43] including a meta-analysis of outbreaks (73% overall effectiveness after 1 dose).[27] The results were also in accordance with previous publications on the impact of vaccination in Germany,[44,45] where effectiveness of 1 dose of varicella vaccination was reported as 71%, with nonsignificant vaccine-specific differences (OKA/GSK: 56%, OKA/Merck: 86%, MMR-OKA/GSK: 55%).[45] However, this outbreak investigation had several methodological limitations, for example, the fact that different outbreaks were pooled and there was no laboratory confirmation of varicella disease.[46] Effectiveness of 1 dose of any varicella vaccine against PCR-confirmed varicella infection of any severity and against PCR-confirmed moderate or severe varicella was similar to the case-control study in the United States by Vázquez et al[23] [86.1% (95% CI: 76.9–91.7) versus 85% (95% CI: 78–90) and 97.6% (95% CI: 90.1–99.4) versus 97% (95% CI: 93–99), respectively; unadjusted], who investigated the effectiveness of OKA/Merck. In our study, the effectiveness of OKA/GSK against any varicella disease was lower [70.6% (95% CI: 47.7–83.5)], but the effectiveness against moderate or severe varicella was comparably high [94.1% (95% CI: 75.5–98.6)]. In case-control studies from Israel and China based on parent interviews of children clinically diagnosed with varicella (no laboratory confirmation) during a period of still very low coverage, the effectiveness data of OKA/GSK were slightly higher, 88% (95% CI: 77–94) and 86% (95% CI: 73–93), respectively, than what we found in our setting against laboratory-confirmed varicella.[28,29] This may indicate that in our study the identification of nontypical mild cases of varicella in vaccinated children (with a small number of lesions) was facilitated when compared with other studies.

Varicella vaccination at an early age had been associated with lower vaccine effectiveness in some studies,[24,47] although other studies could not confirm that difference.[28,41,48] In contrast to Vázquez et al,[24] varicella vaccine effectiveness in our study was not lower in children vaccinated at <15 months of age.

Meaning of the Study

The first epidemiological case-control study of the effectiveness of varicella vaccination in a routine setting in Europe provides valuable information on the effectiveness of 1-dose varicella vaccination during a period of up to 5 years after vaccination in a population with vaccination coverage of about 50%. In agreement with the literature, the effectiveness against moderate or severe varicella was high, allowing for the control of severe varicella disease and complications.

Unanswered Questions and Future Research

Additional research is necessary to assess the long-term vaccine effectiveness of 1 or 2 doses of licensed varicella vaccines in Europe.

TRADEMARKS

Varilrix (OKA/GSK) and Priorix Tetra (MMR-OKA/GSK) are registered trademarks of the GlaxoSmithKline group of companies. Varivax (OKA/Merck) is a registered trademark of Merck, Sanofi Pasteur MSD. For pharmaceutical details of each of the vaccines, we refer to the respective manufacturer's product information.

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REFERENCES

1. Heininger U, Seward JF. Varicella. *Lancet*. 2006;368:1365–1376.
2. Wharton M. The epidemiology of varicella-zoster virus infections. *Infect Dis Clin North Am*. 1996;10:571–581.
3. Weinberg JM. Herpes zoster: epidemiology, natural history, and common complications. *J Am Acad Dermatol*. 2007;57(suppl 6):S130–S135.
4. Wutzler P, Färber I, Wagenpfeil S, et al. Seroprevalence of varicella-zoster virus in the German population. *Vaccine*. 2001;20:121–124.
5. Liese JG, Grote V, Rosenfeld E, et al.; ESPED Varicella Study Group. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *Pediatr Infect Dis J*. 2008;27:119–124.
6. Rack AL, Grote V, Streng A, et al. Neurologic varicella complications before routine immunization in Germany. *Pediatr Neurol*. 2010;42:40–48.
7. Grote V, von Kries R, Springer W, et al. Varicella-related deaths in children and adolescents--Germany 2003–2004. *Acta Paediatr*. 2008;97:187–192.
8. Marin M, Zhang JX, Seward JF. Near elimination of varicella deaths in the US after implementation of the vaccination program. *Pediatrics*. 2011;128:214–220.
9. Calendrier Vaccinal Recommandé au Luxembourg. Available at: http://www.sante.public.lu/fr/rester-bonne-sante/120-vaccinations/calendrier-vaccinal/index.html. Accessed March 6, 2012.
10. Boletin Epidemiológico de la Comunidad de Madrid. *Varicela en la Comunidad de Madrid, Años 2001 a 2009.* 2010; 16:3–22.
11. Alfonsi V, D'Ancona F, Giambi C, et al.; Regional Coordinators for Infectious Diseases and Vaccinations. Current immunization policies for pneumococcal, meningococcal C, varicella and rotavirus vaccinations in Italy. *Health Policy*. 2011;103:176–183.
12. Bonanni P, Breuer J, Gershon A, et al. Varicella vaccination in Europe - taking the practical approach. *BMC Med*. 2009;7:26.
13. Quian J, Rüttimann R, Romero C, et al. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997-2005. *Arch Dis Child*. 2008;93:845–850.
14. Reuss AM, Feig M, Kappelmayer L, et al. Varicella vaccination coverage of children under two years of age in Germany. *BMC Public Health*. 2010;10:502.
15. Gavrielov-Yusim N, Battat E, Neumann L, et al. Birth order and private voluntary immunization–a study of 110,902 children. *Vaccine*. 2012;30:442–447.
16. Robert Koch Institut. Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch Institut/Stand: Juli 2004. *Epidemiol Bull*. 2004;30:235–250.
17. Streng A, Seeger K, Grote V, et al. Varicella vaccination coverage in Bavaria (Germany) after general vaccine recommendation in 2004. *Vaccine*. 2010;28:5738–5745.
18. Hohle M, Siedler A, Bader HM, et al. Assessment of varicella vaccine effectiveness in Germany: a time-series approach. *Epidemiol Infect*. 2011;139:1710–1719.
19. Robert Koch Institut. Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch Institut/Stand: Juli 2009. *Epidemiol Bull*. 2009;30:279–298.
20. Chaves SS, Zhang J, Civen R, et al. Varicella disease among vaccinated persons: clinical and epidemiological characteristics, 1997–2005. *J Infect Dis*. 2008;197(suppl 2):S127–S131.
21. Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance sites--United States, 1995–2005. *J Infect Dis*. 2008;197(suppl 2):S71–S75.
22. Shah SS, Wood SM, Luan X, et al. Decline in varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against varicella. *Pediatr Infect Dis J*. 2010;29:199–204.
23. Vázquez M, LaRussa PS, Gershon AA, et al. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med*. 2001;344:955–960.
24. Vázquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. *JAMA*. 2004;291:851–855.
25. Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011;203:312–315.
26. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis*. 2008;197(suppl 2):S82–S89.
27. Bayer O, Heininger U, Heiligensetzer C, et al. Metaanalysis of vaccine effectiveness in varicella outbreaks. *Vaccine*. 2007;25:6655–6660.
28. Sheffer R, Segal D, Rahamani S, et al. Effectiveness of the Oka/GSK attenuated varicella vaccine for the prevention of chickenpox in clinical practice in Israel. *Pediatr Infect Dis J*. 2005;24:434–437.
29. Fu C, Wang M, Liang J, et al. The effectiveness of varicella vaccine in China. *Pediatr Infect Dis J*. 2010;29:690–693.
30. Bavarian Statistical Office. Available at: https://www.statistik.bayem.de. Accessed March 6, 2012.
31. Mols JF, Ledent E, Heineman TC. Sampling of herpes zoster skin lesion types and the impact on viral DNA detection. *J Virol Methods*. 2013;188:145–147.
32. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med*. 2007;356:1121–1129.
33. Niccolai LM, Ogden LG, Muehlenbein CE, et al. Methodological issues in design and analysis of a matched case-control study of a vaccine's effectiveness. *J Clin Epidemiol*. 2007;60:1127–1131.
34. Michalik DE, Steinberg SP, LaRussa PS, et al. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. *J Infect Dis*. 2008;197:944–949.
35. Marin M, Güris D, Chaves SS, et al.; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40.
36. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. *Pediatrics*. 2008;122:e744–e751.
37. Shapiro ED. Case-control studies of the effectiveness of vaccines: validity and assessment of potential bias. *Pediatr Infect Dis J*. 2004;23:127–131.
38. Chaves SS, Lopez AS, Watson TL, et al. Varicella in infants after implementation of the US varicella vaccination program. *Pediatrics*. 2011;128:1071–1077.
39. Skull SA, Wang EE. Varicella vaccination–a critical review of the evidence. *Arch Dis Child*. 2001;85:83–90.
40. Passwell JH, Hemo B, Levi Y, et al. Use of a computerized database to study the effectiveness of an attenuated varicella vaccine. *Pediatr Infect Dis J*. 2004;23:221–226.
41. Arnedo-Pena A, Puig-Barberà J, Aznar-Orenga MA, et al. Varicella vaccine effectiveness during an outbreak in a partially vaccinated population in Spain. *Pediatr Infect Dis J*. 2006;25:774–778.
42. Miron D, Lavi I, Kitov R, et al. Vaccine effectiveness and severity of varicella among previously vaccinated children during outbreaks in day-care centers with low vaccination coverage. *Pediatr Infect Dis J*. 2005;24:233–236.
43. Quian RJ, Protasio PA, Dall'orso VP, et al. Varicella outbreak in a village in Uruguay. *Rev Chilena Infectol*. 2010;27:47–51.
44. Siedler A, Arndt U. Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. *Euro Surveill*. 2010;15:19530.
45. Spackova M, Wiese-Posselt M, Dehnert M, et al. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. *Vaccine*. 2010;28:686–691.
46. Marchetti F, Cuccia M. The effectiveness of Varivax and Varilrix vaccines. *Vaccine*. 2010;28:4859–4860.
47. Verstraeten T, Jumaan AO, Mullooly JP, et al.; Vaccine Safety Datalink Research Group. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics*. 2003;112:e98–103.
48. Outbreak of varicella among vaccinated children--Michigan, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:389–392.

