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Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain

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Varicella vaccine effectiveness was evaluated in a case-control study in Navarre, Spain, in 2010–2012. The cases were 54 children aged 15 months to 10 years with a diagnosis of varicella confirmed by polymerase-chain-reaction. Each case was matched with eight controls by pediatric practice, district of residence and date of birth. The effectiveness was 87% (95% confidence interval: 60% to 97%) for one dose of vaccine and 97% (80% to 100%) for two doses. A single dose was 93% (34% to 100%) effective in the first year, which declined to 61% (95% CI: -64% to 94%) after the third year. In conclusion, varicella vaccine is highly effective in preventing confirmed cases, although this effect declines over time since the first dose. A second dose helps to reestablish very high levels of effectiveness and to reduce the risk of breakthrough varicella.

Introduction

In the absence of vaccination, varicella virus circulates widely and infects most people during childhood.[1] In 1995 the first varicella vaccine was introduced in the US childhood vaccination schedule with one dose. Subsequent years have seen a reduction in the cases of varicella.[2,3] This vaccine showed good short-term efficacy in clinical trials,[4] and in the first observational studies.[5-7] Over time, however, continued outbreaks in highly vaccinated populations and an increasing number vaccine failures[3,8-11] led to the recommendation of a second dose.[12,13] Higher antibody titers are achieved with a second dose of varicella vaccine,[14] which suggests greater and longer lasting protection. Vaccination schedules with one and two doses currently coexist, but few studies have evaluated the effectiveness of vaccination with two doses in preventing confirmed cases of varicella.[15-17]

In Navarre, Spain, varicella vaccine had been marketed since 2004. Initially, a single dose at 15 mo was recommended by pediatricians,[18] and parents could choose to have their children vaccinated if they paid for it. Coverage increased to 19% of children aged 1 to 5 y in 2006. In 2007, universal varicella vaccination was introduced into the childhood vaccination schedule with one dose of Varivax® (Oka/Merck) applied at 15 mo, and beginning in 2009 the second dose was added at 3 y of age. In the period 2009–2011 vaccination coverage was around 95% for the first dose and over 89% for the second dose. Children not previously vaccinated who had not had varicella were also offered vaccination at 3 y and 10 y of age.[19]

The objective of this study was to evaluate the effectiveness of varicella vaccine in preventing confirmed cases by comparing the one- and two-dose schedules.

Results

During the study period, the participating pediatricians reported 70 clinical cases of varicella in children aged 15 mo to 10 y, which were tested by real-time polymerase chain reaction (PCR), and 54 (77%) of them were confirmed for varicella virus. No cases required hospitalization or presented complications of varicella. There were no differences among positive and negative patients in the characteristics evaluated, apart from the varicella vaccination status. Among unvaccinated children, 89% were confirmed for varicella virus as compared with 38% of vaccinated children ($p < 0.001$).

Each confirmed case was matched by pediatric practice, district of residence and date of birth (± 1 y) with eight controls. Cases (n = 54) and controls (n = 432) were distributed almost equally in terms of age and birth year. No differences were found by sex or by history of any major chronic condition. Visits to the pediatrician in the previous 12 mo and having migrant parents were somewhat more frequent among cases, therefore it was decided to adjust for these two variables in the multivariate models (**Table 1**).

Some 26% of controls had received one dose of varicella vaccine and 15% had received two doses, compared with 9% and 2% of cases, respectively ($p < 0.001$). However, cases and controls

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Table 1. Characteristics of cases and controls

	Cases	Controls	p-value
	N (%)	N (%)	
Sex			0.067
Male	21 (39%)	225 (52%)	
Female	33 (61%)	207 (48%)	
Age			0.998
15–24 mo	6 (11%)	48 (11%)	
3–4 y	7 (13%)	59 (14%)	
5–6 y	9 (17%)	67 (16%)	
7–8 y	26 (48%)	214 (50%)	
9–10 y	6 (11%)	44 (10%)	
Major chronic condition			0.487
No	47 (87%)	360 (83%)	
Yes	7 (13%)	72 (17%)	
Other persons in the household			0.124
1	4 (7%)	41 (9%)	
2	5 (9%)	96 (22%)	
3	24 (44%)	164 (38%)	
4+	21 (39%)	131 (30%)	
Migrant parents			0.019
No	42 (78%)	384 (89%)	
Yes	12 (22%)	48 (11%)	
Visits to the pediatrician			0.050
0	3 (6%)	73 (17%)	
1–5	30 (56%)	239 (55%)	
6+	21 (39%)	120 (28%)	
Doses of varicella vaccine			< 0.001
0	48 (89%)	257 (59%)	
1	5 (9%)	112 (26%)	
2	1 (2%)	63 (15%)	
Doses of measles-mumps-rubella vaccine			0.766
0	2 (4%)	26 (6%)	
1	14 (26%)	103 (24%)	
2	38 (70%)	303 (70%)	
Total	54 (100%)	432 (100%)	

did not differ in coverage with one and two doses of MMR vaccine (p = 0.766) (**Table 1**).

Vaccination status varied with age. A total of 75% of controls younger than 3 y had been vaccinated, 80% of those aged 3–4 y, 49% of those aged 5–6 y and 23% of children aged 7 or older. The median time since vaccination was 22 mo among the controls who had received one dose of vaccine and 17 mo in those who had received two doses.

Six vaccine failures were confirmed by PCR, and one of them had received two doses of vaccine. The time between the last dose and diagnosis of varicella ranged between 35 weeks and 6 y, and the age at diagnosis between 2 and 8 y. Only one person had been diagnosed with a major chronic condition. The only vaccine failure with two doses occurred in a child with no major chronic conditions who had received the second dose of vaccine 48 weeks before being diagnosed with varicella.

In the conditional logistic regression analysis the effectiveness of any dose of vaccine was 92% (95% CI: 77% to 97%). Having received a single dose of vaccine showed an effectiveness of 87% (95% CI: 60% to 97%), and the effectiveness of two doses was 97% (95% CI: 80% to 100%). Similar findings were found in the analysis restricted to children aged 3 y or more (**Table 2**). Two doses conferred an incremental protection of 74% (95% CI: -115% to 100%; p = 0.231) as compared with one dose, although this result was not statistically significant.

Among those vaccinated with a single dose, the effectiveness was 93% (95% CI: 34% to 100%) in the first 12 mo after vaccination, 95% (95% CI: 62% to 100%) between 12 and 35 mo after vaccination, and 61% (95% CI: -64% to 94%) after 35 mo (**Table 2**). The time after vaccination as a continuous variable in years was associated with an increased risk of breakthrough varicella among children who had received a dose of vaccine (OR = 2.07, 95% CI: 1.13–3.80, p = 0.019) (**Table 3**).

Discussion

The results of this study show that the varicella vaccine is effective in preventing confirmed cases of varicella, although the effect of this vaccine depends on the number of doses and the time since the last dose. Vaccine effectiveness was 87% for one dose and 97% for two doses. The results suggest that the second dose of vaccine increases the effectiveness with respect to the first dose, although this result did not reach statistical significance. These findings are similar to those of other authors. In a literature review, Seward et al. found a mean effectiveness for one dose of vaccine of 84.5%, with a range of 44% to 100%.[3] Shapiro et al. estimated a 98.3% effectiveness for two doses of vaccine in preventing laboratory-confirmed cases.[15] Our estimation of the incremental effect of the second dose as compared with the first is also within the range of what other authors have found;[15-17] however, the large differences found among these studies show that the incremental effect of the second dose is a relative measure that may vary depending on the situation in which it is evaluated.

The effectiveness of a single dose of varicella vaccine was very high during the first three years (> 90%) and fell in children who had been vaccinated more than three years previously (61%), which supports the role of waning immunity as an explanation of the suboptimal effectiveness of a single dose of varicella vaccine.[8,20] In Navarre the loss of effectiveness was more pronounced than in other studies,[8] although the wide confidence intervals mean that no conclusions can be drawn in this respect. This loss of effectiveness may have been facilitated by the fact that circulation of the varicella-zoster virus also declined considerably during the study period,[19] with the consequent reduction of the booster effect from repeated exposure to wild virus.

Most children with two doses of varicella vaccine had received the last dose recently, and only one clinical case with two doses was confirmed by the laboratory, which made it impossible to determine if there is an important loss of effectiveness over time.

Table 2. Estimates of the effectiveness of varicella vaccine in different analyses

Varicella vaccine status	Cases/ controls	Crude vaccine effectiveness (95% CI)*	Adjusted vaccine effectiveness (95% CI)#	p-value
Unvaccinated	48/257	-	-	
Vaccinated (any dose)	6/175	90% (73%; 96%)	92% (77%; 97%)	< 0.001
Unvaccinated	48/257	-	-	
One dose	5/112	84% (53%; 95%)	87% (60%; 97%)	< 0.001
Two doses	1/63	97% (79%; 100%)	97% (80%; 100%)	< 0.001
Children aged < 3 y				
Unvaccinated	5/12	-	-	
One dose	1/36	93% (31%; 100%)	84% (-58%; 100%)	0.119
Children aged ≥ 3 y				
Unvaccinated	43/245	-	-	
One dose	4/76	78% (30%; 95%)	80% (37%; 95%)	0.003
Two doses	1/63	96% (78%; 100%)	97% (79%; 100%)	< 0.001

* Result of the unadjusted conditional logistic regression model. #Result of the exact conditional logistic regression adjusted for migrant parents and visits to the pediatrician in the previous 12 mo.

Table 3. Estimates of the effectiveness of one dose of varicella vaccine according to time since vaccination

Varicella vaccine status	Cases/controls	Crude vaccine effectiveness (95% CI)*	Adjusted vaccine effectiveness (95% CI)#	p-value
Unvaccinated	48/257	-	-	
< 12 mo after vaccination	1/30	89% (4%; 100%)	93% (34%; 100%)	0.011
12–35 mo after vaccination	1/47	93% (51%; 100%)	95% (62%; 100%)	< 0.001
≥ 36 mo after vaccination	3/35	64% (-42%; 94%)	61% (-64%; 94%)	0.271

*Result of the unadjusted conditional logistic regression model. #Result of the exact conditional logistic regression adjusted for migrant parents and visits to the pediatrician in the previous 12 mo.

Moreover, the incremental effect of the second dose may be overestimated, given that the average time since the last dose was longer in children who had received only one dose of vaccine than in those who had received two, therefore the latter had less time to develop waning immunity. The same phenomenon may have affected other studies that have evaluated the incremental effect of the second dose of vaccine.[15,16] The effectiveness that we found for the second dose is similar to that observed in the two years following the administration of the first dose, which suggests the usefulness of continued monitoring of the effectiveness of the second dose over the longer term.

Among the strengths of this study are the restriction to laboratory-confirmed cases, since the proportion of PCR-negative cases was higher among vaccinated children, and the fact that it was performed during the period the vaccine was being introduced, when there were large proportions of both vaccinated and unvaccinated children of different ages. However, it also has several limitations. The number of study subjects was small and the confidence intervals of the estimates were wide due to the major decline in incidence after the introduction of vaccination with two doses.[19] Accordingly, all the results should be viewed with caution. Not all pediatricians participated in taking samples for laboratory confirmation of cases, although those who did took samples from all patients with clinical signs of varicella, which avoids selection bias due to vaccination status. Clinical cases that were negative for varicella virus were excluded from the study. Although the sensitivity of PCR is high, we cannot totally rule out a bias for the exclusion of false-negative results for varicella virus. In the matched analysis, only case-control pairs discordant for vaccination status provide information. To improve the power of the study we included eight controls per case, which provided more opportunities to have case-control pairs that contributed to the estimation of vaccine effectiveness.

Case-control studies may be subject to bias in the selection of controls. Coverage of MMR vaccine was similar in cases and controls, which seems to rule out this bias, given that both the MMR and varicella vaccines are administered to children at similar ages.

Vaccine failures occurred in children with both one and two doses of vaccine. Cases of breakthrough varicella are usually mild, with few lesions; therefore they can be confused with other causes. In a context of universal vaccination and low incidence, virological confirmation is essential to avoid including false cases which would lead to an underestimate of vaccine effectiveness.

In conclusion, varicella vaccine is highly effective in preventing confirmed cases, although this effect declines over time since the first dose. The administration of a second dose helps to reestablish very high levels of effectiveness and to reduce the risk of breakthrough varicella. However, it is desirable to continue monitoring the duration of the effectiveness of two doses of varicella vaccine over time.

Materials and Methods

The present matched case-control study was conducted in Navarre, Spain, using information from health care computerized databases. Varicella surveillance is based on automatic reporting of all clinical cases from the clinical records databases of hospitals and primary health care. Since May 2010, varicella surveillance has incorporated a protocol for laboratory confirmation of cases. Twenty-nine primary care pediatricians agreed to adhere to this protocol by taking a vesicle swab from all cases of varicella, after receiving parental consent. Samples were collected with a polyester swab, placed in transport medium and maintained at ambient temperature until delivery to the laboratory. DNA was extracted from clinical samples using an automated platform (Biorobot EZ1-Qiagen). Real time polymerase-chain-reaction assay was performed in Smart Cycler, and Smart varicella-zoster virus reactive (Cepheid) was used for DNA detection.

In this study, the cases were children aged 15 mo to 10 y who were diagnosed with varicella confirmed by PCR between May 1, 2010 and June 30, 2012. From the primary care database of clinical records, eight anonymous controls were selected for each case from children with no previous diagnosis of varicella, matched with the cases by pediatric practice, district of residence and date of birth (± 1 y). From all controls who met these eligibility criteria, we consecutively selected those whose date of birth was closest to that of the case, preferably among those born in the same calendar year. The number of doses and date of administration of the varicella and measles-mumps-rubella (MMR) vaccines were taken from the Navarre vaccination registry for both the cases and controls. From the clinical documentation of cases and controls we obtained information on the sex, date of birth, pediatrician, district and municipality of residence, major chronic conditions (cardiovascular disease, respiratory disease, diabetes, neurological disease, renal disease or cancer), migrant parents and the number of visits to the pediatrician in the previous 12 mo. These last two variables were included as indicators of health care seeking behaviors. Varicella cases occurring more than 42 d after administration of a dose of varicella vaccine were considered vaccine failures or breakthrough varicella.

We evaluated the effect of having received any dose of varicella vaccine and also of having received specifically one or two doses. After excluding children who had received two doses of vaccine, we evaluated the effect of one dose, according to time since vaccination as a categorical and as a continuous variable.

Unmatched dichotomous variables were compared by χ^2. Matched odds ratio (OR) for vaccination, with their 95% confidence interval (CI), was calculated with conventional or exact conditional logistic regression models adjusted for potential confounding. Vaccine effectiveness was estimated as a percentage: (1-OR) × 100.

The Navarre Ethical Committee for Medical Research approved the study protocol.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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