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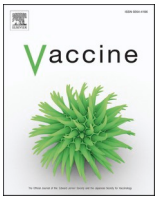

A population database analysis to estimate the varicella vaccine effectiveness in children < 14 years in a high vaccination coverage area from 2004 to 2022

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ABSTRACT

Introduction: In the Veneto Region of Italy, universal varicella vaccination (VV) started in 2007 with a two-dose schedule at 12–15 months and 5–6 years of age achieving 90 % coverage in 2019. The study aimed at evaluating the vaccine effectiveness (VE) in children using a primary-care database

Methods: This retrospective analysis used Pedianet, a comprehensive database of 73 family paediatricians in the Veneto Region. Incidence rates (IR) of varicella were evaluated in children aged <14 years enrolled since birth, between January 2004 to April 2022. Cases were classified as breakthrough if happening beyond 42 days post-VV. Complications and prescription were evaluated. Subject were followed up from 2004 or the enrollment date, until the end of assistance/study or the first or second VV dose. Kaplan-Meier curves and log-rank tests were used to compare the varicella incidence by vaccination status. Hazard ratios of varicella infection, adjusted (aHRs) for sex, vaccinal status, age group, prematurity and socioeconomic status were estimated with Cox's regression. VE for one and two VV doses was defined as 1-aHR*.

Results: 36,498 children, followed for 233,508 person-years from 2004 to 2022 experienced 1006 cases of varicella (13 complicated and 35 breakthrough). Younger children had a higher risk of experiencing varicella compared to children aged >7 years, irrespective of their vaccination status. Indeed, the IR increased from 5.5 to 19.5 × 1000 person-years and from 1.1 to 5.4 × 1000 person-years in unvaccinated and vaccinated children aged <12 months versus those aged 5–6 years, respectively. Varicella VE was 83.4 % and 94.7 % in those vaccinated with one and two doses. After six years, the cumulative probability of experiencing varicella was 10.7 % for unvaccinated subjects, and 2.5 % and 0.4 % for those vaccinated with one and two-doses (log-rank test, $p < 0.001$).

Conclusions: Two-dose schedule VV is effective in drastically reduce varicella episodes. Breakthrough varicella episodes remain rare events.

1. Background and rationale

The introduction of routine childhood varicella immunization has dramatically changed the epidemiological landscape of the disease, resulting in reduced disease incidence, complications, hospital admissions, and deaths in children and in the general population. These outcomes highlight the establishment of robust herd immunity.

In Italy, after conducting an experimental phase in eight regions starting in 2013, the universal varicella vaccination program was officially launched in 2017. This initiative targeted all children, with a two-dose vaccination schedule administered at 12–15 months of age and 5 to 6 years of age. [1] As of 2019, Italy achieved a vaccination coverage rate of 90.50 % for varicella, as indicated by a 24-month follow-up of the 2017 cohort. However, variations were noted among different regions.

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Epidemiological data underscore a notable reduction in varicella incidence, with a nearly 50 % decrease in reported episodes from 2003 to 2013. [2]

Nevertheless, breakthrough varicella (BV) infections can occur following exposure to the wild-type varicella-zoster virus in individuals previously vaccinated, potentially arising from either primary or secondary vaccine failure. [3] BV is usually mild, with a reduced risk of complications. Studies indicate an average incidence of BV at 8.5 cases per 1000 persons per year following the initial dose [4], with an estimated 20 % of children susceptible to developing varicella disease [5]. Primary vaccine failure is observed in less than 1 % of individuals who receive two doses, offering superior protection compared to a single dose and eliciting a prolonged antibody response lasting over ten years [6].

Administrative electronic health record databases are mainly used for administrative and reimbursement purposes and primarily capture information on diagnoses at the hospital and ER levels and therefore are limited in capturing varicella episodes in Italy [7]. Moreover, also standard national notifiable diseases surveillance system are limited because based on active notification by clinicians and may be subject to underreporting [8]. We aimed to assess the residual burden of varicella disease and assess varicella vaccine effectiveness in the paediatric population using a primary-care database over the past two decades.

2. Methods

This population-based birth cohort analysis was compliant with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance methodological standards and did not require an Ethics Committee approval.

2.1. Data source

The Pedianet database was used as the source of the study. Pedianet is a national population database that contains anonymous patient-level data of more than 500,000 children since 2004, corresponding to around 4 % of the annual paediatric population, who received healthcare from 193 family paediatricians (FPs) from January 1st, 2004, to April 30th,2022 in Italy who were part of the Pedianet network using the same software (Junior Bit®, Padova, Italy) in their professional practice. For this study, only data from children residing in the Veneto region were extracted on October 23rd, 2022.

According to the Italian NHS, each child is assigned to a FP who is the primary referral for health-related matters. In Italy, there is a tax-funded public healthcare system with universal access, and patients do not incur in any direct costs related to primary care visits. The Pedianet database captures several types of patient-level information, including the reason for accessing healthcare, health status, demographic data, diagnosis and clinical symptoms (free text or ICD-9CM codes), drugs (Anatomical-Therapeutical-Chemical codes), specialist appointments, diagnostic procedures, hospital or emergency room (ER) admissions, growth parameters, and clinical outcome data. Informed consent is required from children's parents to enter the data in the database. The data collected from the child's parents/tutors by paediatricians enters the dedicated cloud already encrypted and anonymized. Pedianet researchers do not know the anonymization process and cannot know the owner of the data in any way.

2.2. Study design and study population

This is a retrospective population-based birth cohort database analysis aiming at assessing the variation in the incidence of varicella over calendar years between 2004 and 2022 in children <15 years of age. Any subjects with missing data on age or sex or not enrolled in the database since birth were excluded. Moreover, subjects with a first dose of vaccine before 12 months of age, a second dose before 5 years of age, or those with three doses of vaccine were excluded because not compliant with the National Immunization calendar reccomendations [1].

2.3. Exposure and outcomes ascertainment

The exposure of interest was the varicella vaccination. The varicella vaccination was retrieved from the regional immunization database, where all vaccinations are recorded for administrative purposes. All ATC codes (Anatomical Therapeutic Chemical), including a varicella antigen, were considered (J07BK01, J07BD54).

The primary outcome of the study is varicella episodes. The varicella diagnoses were collected with ICD9-CM codes (052.0–052.9) or as free text in the medical notes (in Italian varicella) and manually validated to exclude false positives. Each visit, treatment and medical resource registered within 30 days from the varicella incident date were considered part of the same episode. Cases of varicella within 42 days from vaccination were not considered [9].

A breakthrough varicella case was defined as a diagnosis of varicella that was more than 42 days post-vaccination. [9]

Complications were associated with the varicella episode if a diagnosis of pneumonia, skin and soft tissue infection, neurological complications, and hepatitis (Table 1 in the supplementary) was recorded as outpatient or inpatient visits within 30 days from the varicella episode index date. Every death event (not categorized as accidental death or suicide) was retrieved from the clinical diary and diagnosis field and was associated with the varicella episode if the event was recorded within 30 days from the varicella episode index date. The index date for these outcomes was the date of the diagnosis reported by the FPs or the date of the hospitalization or ER visit if the outcome was not diagnosed by the FP.

Secondary outcomes included the prescriptions for systemic and topical antibiotics (ATC J01* and D06A*, D06C*) and acyclovir (ATC J05AB01). These were associated with the varicella episode if a prescription was recorded within 30 days from the varicella episode index date.

2.4. Statistical analysis

Descriptive analyses were summarized through tabulation and graphical representation of the means, medians, and standard deviations for continuous variables, and frequency distributions for categorical variables.

Each subject was followed from the 15th of the month of birth, until the end of assistance or the first varicella diagnosis or until April 30th 2022, whichever came first.

Incidence rates (IR) of varicella episodes were calculated according to the age group (<12 months, 12-15 months, 16 months-4 years, 5-6 years, 7–13 years) and vaccination status (not vaccinated, vaccinated with one dose and vaccinated with two doses) by dividing the number of varicella episodes during the follow-up period by the total person-time. Person time in vaccinated children was right-truncated 41 days after the date of the first or second VV. The 42-day timeframe provided the recipient with sufficient time to develop immunity to the vaccine.

The timing of the comorbidities inception with respect to vaccination was not known, so only prematurity was considered.

Hazard ratios of varicella infection in the study period, adjusted (aHRs) for sex, vaccinal status, age group, prematurity, and area deprivation index (ADI), a proxy for the socioeconomic status) overall and stratified by age group was estimated with the Cox's regression. 95 % confidence intervals (95 %CI) were estimated [10]. The ADI, computed at the census block level retrieved from the 2011 Italian Census [11], is a socioeconomic measure measured from 1 (lowest deprivation) to 5 (highest deprivatiom). It was calculated based on five parameters: low education, unemployment, living on rent, crowded households, and single-parent families [12]. The socioeconomic status is

Table 1
Descriptive analyses, incidence rates and adjusted Hazard Ratios (aHR) with relative 95 % confidence intervals of children with varicella by variable of interest. Pedianet, 2004–2022.

	Subjects		Follow-up (person-years)		N of Varicella cases	IR (x1,000 person-years)	Cox's regression	
	N	%	Total	Average			aHR (95 %CI)	*P* value
Total	36,498	100	233,508	6.4	1006	4.31		–
Sex								
Males	18,734	51.3	119,980	6.4	538	4.48	1.09 (0.97; 1.24)	0.153
Females	17,764	48.7	113,528	6.4	468	4.12	ref	
Prematurity								
yes	1474	4	7275	4.9	25	3.44	0.84 (0.57; 1.25)	0.396
no	35,024	96	226,233	6.5	981	4.34	ref	
Age group								
<1 year	36,498	100	34,943	1	191	5.47	0.76 (0.56; 1.04)	0.088
12-15 months	33,307	91.3	10,822	0.3	91	8.41	2.18 (1.50; 3.18)	**<0.001**
16 months-4 years	32,050	87.8	94,785	3	468	4.94	2.11 (1.61; 2.76)	**<0.001**
5-6 years	20,445	56	35,754	1.7	179	5.01	3.44 (2.56; 4.63)	**<0.001**
7-13 years	15,445	42.3	57,205	3.7	77	1.35	ref	
Vaccinal status at the end of the follow-up*								
0 dose	36,498	100	69,231	1.9	658	9.5	ref	
1 dose	29,466	80.7	103,223	3.5	313	3.03	0.17 (0.14; 0.19)	**<0.001**
2 doses	15,517	42.5	61,055	3.9	35	0.57	0.05 (0.04; 0.08)	**<0.001**
Area deprivation index								
1 -Least deprived	7456	20.4	47,565	6.4	233	4.9	ref	
2	7509	20.6	49,445	6.6	252	5.1	1.03 (0.87; 1.24)	0.708
3	6888	18.9	44,757	6.5	179	4	0.81 (0.67; 0.99)	**0.039**
4	6093	16.7	39,143	6.4	153	3.91	0.81 (0.66; 1.00)	0.05
5 - Most deprived	5573	15.3	34,212	6.1	142	4.15	0.9 (0.73; 1.11)	0.324
NA	2979	8.2	18,387	6.2	47	2.56		

* For vaccination status at the end of follow up subjects were counted multiple times if belonging to different categories.

an important factor to consider because for specific vaccines (notably for measles, mumps, and rubella), it was observed that the uptake was lowest among the most affluent [13]. To calculate and to compare the varicella incidence by vaccinal status, life-table analysis using the Kaplan-Meier method and log-rank tests were used [14,15]. Vaccine effectiveness (VE) was then evaluated for one and two vaccine doses and defined as 1-HR*100 and the relative 95 %CI.

Prescriptions were reported as numbers and frequency for the overall cohort and divided by vaccinal status and by age group. The variation in the prescription rate was assessed using the Chi-square test. A *p*-value <0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS Statistics, version 28.0.

3. Results

3.1. Population description

A total of 36,498 children with documented vaccination records were followed for 233,508 person-years (equivalent to 6.4 person-years) from 2004 to 2022 (Fig. 1). Among them, 1006 cases of varicella were recorded, accounting for 2.8 % of the subjects, with no discernible difference by sex. Of the subjects with at least one varicella case, 2.5 % were premature (Table 1). At the end of the observation period, 42.5 % of children received complete vaccination (two doses), 38.2 % received one dose, and 19.3 % were unvaccinated (Fig. 1).

Among the 1006 varicella cases, 13 presented complications. Specifically, nine complications occurred among the unvaccinated group (comprising three cases related to skin diseases, three to respiratory diseases, and three unspecified conditions), three occurred among those vaccinated with one dose (involving one case related to skin diseases, one to respiratory diseases, and one unspecified condition), and one complication occurred among those vaccinated with two doses (related to skin diseases). No deaths associated with the varicella event were reported in the population considered.

3.2. Incidence rate and risk of being infected with varicella according to risk factors

Among the unvaccinated, the IR increased up to 6 years of age, from 5.5 in children <12 months to 19.5 varicella cases x 1000 person-years in those aged 5–6 years. (Table 2). Among the children vaccinated with one dose, the IR, even if greatly reduced compared to the unvaccinated peers, increased as well up to 6 years of age, from 1.1 in children aged 12–15 months to 5.4 varicella cases x 1000 patient-years in those aged 5–6 years (Table 2).

With respect to the age group, younger children had a higher risk of experiencing varicella compared to children >7 years of age, according to their vaccination status. In the overall population, varicella VE was 83.4 % in those vaccinated with one dose (aHR [95 %CI]: 0.17 [0.14–0.19], $p < 0.001$] and 94.5 % in those with two doses (aHR [95 % CI]:0.05 [0.04–0.08], $p < 0.001$) (Table 1). Indeed, in 15,517 subjects who received two doses, only 35 breakthrough cases were documented (Fig. 1 and Table 1). When considering the VE stratified by age group, VE decreased with increasing of age from 91 % to 49 % in those who received one-dose. One-dose vaccination was estimated to effectively prevent varicella episodes compared to unvaccinated peers, except in the 7–13 age group (Table 3). The VE for two doses was 98 % and 89 % for children aged 5–6 and 7–13, respectively, showing effectiveness in preventing varicella episodes compared to unvaccinated peers (Table 3).

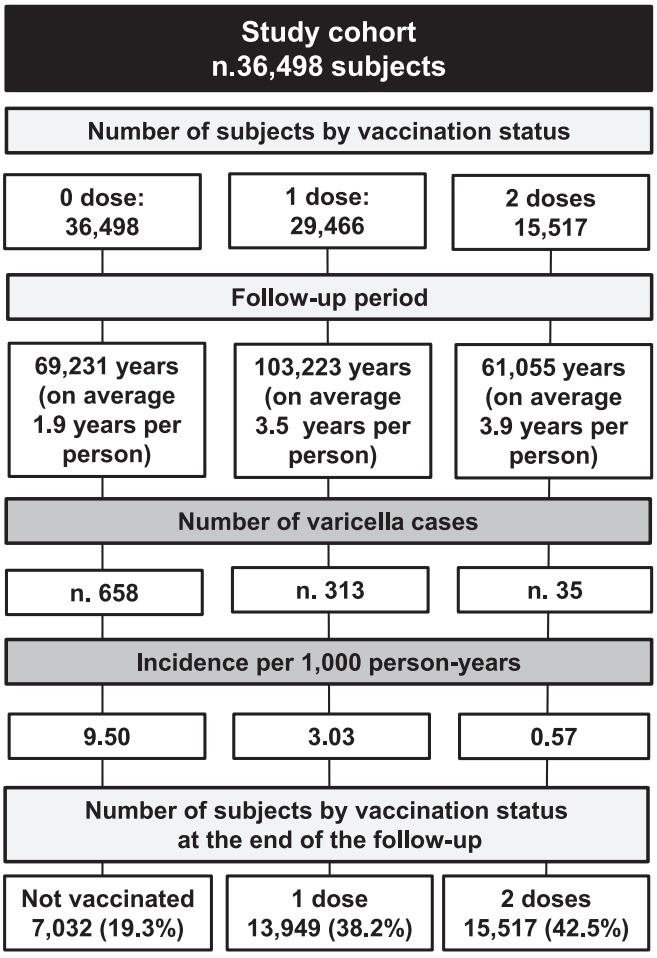

Fig. 1. Flow-chart, follow-up, and varicella cases among the cohort, by vaccination status. Pedianet, 2004–2022.

3.3. Cumulative probability of experiencing varicella according to vaccination status

After two years of follow-up, the probability of experiencing varicella was 1.9 % for unvaccinated children, 0.3 % for those vaccinated with one dose, and 0.1 % for those fully vaccinated (Fig. 2). After six years of follow-up, the probability of experiencing varicella increased to 10.7 % for unvaccinated subjects, to 2.5 % for those vaccinated with one dose and to 0.4 % for those vaccinated with two doses with significative difference (Kaplan-Mayer log-rank test p-value <0.001) (Fig. 2). Specifically, for subjects vaccinated with two doses, the cumulative probability of experiencing varicella remains stable over time, varying from 0.1 % after two years to 0.4 % after eight years of follow-up.

3.4. Antimicrobial prescription for varicella by vaccination status

Of the 1006 subjects who had varicella, 24.2 % had at least one antimicrobial prescription, for a total of 298 prescriptions. Specifically, 10.1 % had a systemic antibiotic prescription, 14.0 % had acyclovir prescribed, and 2 % had a topical antimicrobial prescribed. Unvaccinated received more acyclovir prescriptions compared to vaccinated children with one dose (20.4 % vs 2.2 %, $p < 0.001$) and with two doses (20.4 % vs 0 %) (Table 4). Medicine prescriptions stratified by age class and by vaccination status at the time of varicella are reported in the Supplementary (Table 2s, 3s and 4s) and the differences in prescription prevalences remained similar.

4. Discussion

Assessing the protective effectiveness over time of a vaccine using real-world data is critical to monitor and inform vaccine policy programs [16]. Indeed, the ideal conditions under which clinical trials are conducted are not always met in real life. In addition, subjects with underlying medical conditions, pregnant people, and children are often excluded from trials, even though those subjects might be at a higher risk of severe disease from varicella. This and other factors, such as the short duration of trials, may impair the generalizability of the results [17].

In our population, younger children had a higher risk of experiencing varicella compared to children >7 years of age, according to their vaccination status. However, the incidence rate of varicella in younger unvaccinated children was almost 10-fold higher than in younger vaccinated (one dose) children, further confirming that toddlers are a crucial target in the varicella vaccination program planning.

We found a varicella VE equal to 83.4 % in those vaccinated with one dose and 94.5 % in those with two doses. Our study confirms and extends the findings of a recent overview of reviews, reporting the pooled estimate of one-dose VE varying from 55 % to 88 % in a non-outbreak setting and from 54 % to 98 % in an outbreak setting and the pooled estimate of two-doses VE varying from 87 % to 95 % (with similar estimates for outbreak setting). [18] As regards severe disease, the evidence suggests that one-dose vaccination strategies are also highly effective against moderate to severe varicella, with effectiveness estimates ranging from 90 % to 100 %. [19–22] Moreover, other studies confirmed the high varicella VE in the paediatric population [23].

As reported by Shapiro et al. [24], there is a significant controversy surrounding the reduced effectiveness of varicella vaccination over time, prompting inquiries into its underlying causes. Indeed, this decline might result from secondary vaccine failure, characterized by waning immunity, or primary vaccine failure, which entails the inability to

Table 2
Incidence rates and breakthrough varicella cases by age group and vaccination status. Pedianet, 2004–2022.

	Total	0 dose			1 dose			2 doses		
	N of subjects	N of cases	Follow-up (person-years)	IR (x1,000 person-years)	N of cases	Follow-up (person-years)	IR (x1,000 person-years)	N of cases (Break-through)	Follow-up (person-years)	IR (x1,000 person-years)
Age class										
<1 year	36,498	191	34,943	5.5						
12-15 months	33,307	87	7033	12.4	4	3789	1.1			
16 months - 4 years	32,050	249	12,553	19.8	219	82,232	2.7			
5–6 years	20,445	86	4408	19.5	85	15,804	5.4	8	15,542	0.5
7–13 years	15,445	45	10,294	4.4	5	1398	3.6	27	45,513	0.6
Total	364,98	658	69,231	9.5	313	103,223	3.0	35	61,055	0.6

Table 3
Adjusted Hazard Ratios (aHR) of varicella infection in the study period stratified by age group with relative 95 % confidence intervals. Pedianet, 2004–2022.

	12-15 m			16 m-4y			5-6y			7-13y		
	aHR	(95 %CI)	p	aHR	(95 %CI)	p	aHR	(95 %CI)	p	aHR	(95 %CI)	p
Sex (M vs F)	0.89	(0.59;1.34)	0.563	1.02	(0.85;1.23)	0.796	1.14	(0.85;1.53)	0.386	1.21	(0.77;1.89)	0.407
Prematurity (yes vs no)	0.57	(0.14;2.33)	0.438	0.97	(0.56;1.69)	0.922	0.68	(0.22;2.15)	0.516	–		
Vaccinal status												
0 dose	ref			ref			ref			ref		
1 dose	0.09	(0.03;0.25)	**<0.001**	0.13	(0.11;0.16)	**<0.001**	0.22	(0.16;0.30)	**<0.001**	0.61	(0.24;1.54)	0.293
2 doses	–			–			0.02	(0.01;0.05)	**<0.001**	0.11	(0.07;0.18)	**<0.001**
Area deprivation index												
1 -Least deprived	ref			ref			ref			ref		
2	1.06	(0.57;1.97)	0.851	0.88	(0.68;1.15)	0.361	1.02	(0.67;1.54)	0.935	1.74	(0.88;3.41)	0.109
3	1.00	(0.53;1.91)	0.991	0.77	(0.58;1.02)	0.068	0.82	(0.53;1.29)	0.397	1.31	(0.63;2.72)	0.474
4	0.77	(0.38;1.59)	0.485	0.74	(0.55;1.00)	0.050	0.82	(0.51;1.32)	0.421	1.16	(0.53;2.53)	0.718
5 - Most deprived	1.38	(0.73;2.61)	0.320	0.89	(0.66;1.21)	0.462	0.73	(0.43;1.24)	0.248	1.10	(0.47;2.58)	0.823

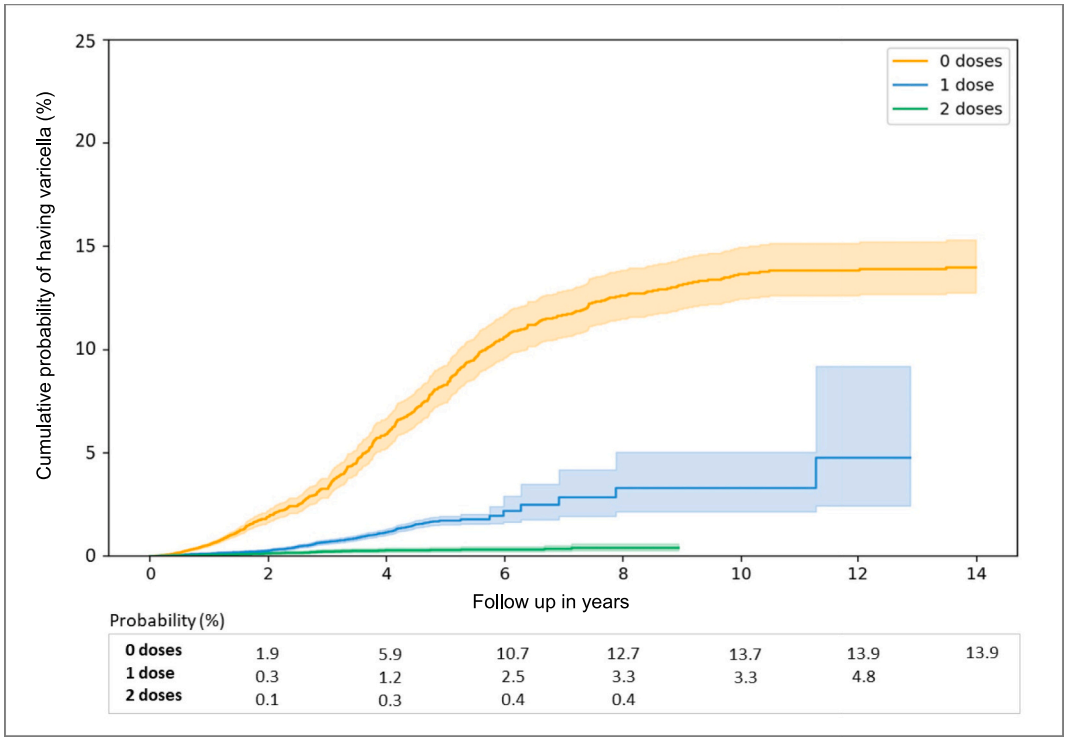

Fig. 2. Kaplan-Mayer curves depicting the cumulative probability of experiencing varicella among unvaccinated (yellow line), vaccinated with one dose (blue line), and vaccinated with two doses (green line) over the years, with 95 % confidence intervals (translucent ribbon). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

induce lasting protection in specific vaccine recipients. The two-dose varicella vaccine seems to provide much higher antibody levels than one-dose within six weeks [25]. We indeed reported the cumulative probability of experiencing varicella after six years of follow-up to be 10.7 % for unvaccinated subjects, 2.5 % for those vaccinated with one dose and 0.4 % for those vaccinated with two doses with significative difference (Kaplan-Mayer log-rank test, $p < 0.001$).

A strength of our study was the use of the Pedianet primary-care database, which allowed us to study a very large population-based cohort, including sociodemographic characteristics, clinical information, and medicine utilization, to evaluate the varicella VE over two decades. Second, given the longevity and the administrative and surveillance use of the immunization registry in the Veneto region, vaccination data are of high standard. Third, our study overcame the limitations of surveillance studies based on prospective data collection, reducing the under-detection of varicella cases. Moreover, we applied a validated algorithm on the clinical note-free text to reduce under-detection.

Our study also had several limitations. First, the study is of a retrospective nature, which, as with any observational study, does not allow for the elimination of the possibility that patients receiving vaccination differ from those who did not receive it for some unmeasured features that the pediatrician did not report in the medical records. Second, the exclusion of children of FPs who did not adhere to the regional vaccination campaign could have affected the study cohort. Third, because the outcome was based on the clinical assessment of the FPs rather than laboratory-confirmed varicella, the estimates of VE may vary based on a subjective evaluation of FPs. Fifth, the vaccine effectiveness should be studied considering also how many susceptible people in a population are vaccinated in a time-period and the effect of the transmission rate in the community. Sixth, we did not analyzed the VE by vaccine type because of missing information regarding the vaccine type in around 40

Table 4
Antimicrobial prescription by vaccination status at the time of varicella and medicine class. Pedianet 2004–2022.

		Varicella cases by vaccination status				
		Unvaccinated (*N* = 658)	**1 dose (*N* = 313)**	**2 doses (*N* = 35)**	**Total (*N* = 1006)**	**p-value (Chi square test)[$]**
		N (%)	**N (%)**	**N (%)**	**N (%)**	
All medication	**N. subjects**	**197 (29.9)**	**41 (13.1)**	**5 (14.3)**	**243 (24.2)**	**(unvaccinated vs 1 dose): <0.001**
	N. prescriptions	243	50	5	298	**(unvaccinated vs 2 doses): <0.001**
	Prescription(s) per subject	1.2	1.2	1.0	1.2	
Systemic antibiotics	**N. subjects**	**66 (10.0)**	**33 (10.5)**	**3 (8.6)**	**102 (10.1)**	ns
	N. prescriptions	83	39	3	125	
	Prescription(s) per subject	1.3	1.2	1.0	1.2	
Penicillins with extended spectrum	N. subjects	33 (5.0)	14 (4.5)	0	47 (4.7)	
Penicillins With beta-lactamase inhibitors	N. subjects	17 (2.6)	11 (3.5)	1 (2.9)	29 (2.9)	
II-gen cephalosporins	N. subjects	1 (0.2)	0	0	1 (0.1)	
III-gen cephalosporins	N. subjects	10 (1.5)	2 (0.6)	0	12 (1.2)	
Macrolides	N. subjects	7 (1.1)	4 (1.3)	1 (2.9)	12 (1.2)	
Other	N. subjects	2 (0.3)	4 (1.3)	1 (2.9)	7 (0.7)	
Acyclovir	**N. subjects**	**134 (20.4)**	**7 (2.2)**	**0**	**141 (14.0)**	**(unvaccinated vs 1 dose): <0.001**
	N. prescriptions	144	8		152	
	Prescription(s) per subject	1.1	1.1		1.1	
Topical antimicrobial	**N. subjects**	**11 (1.7)**	**1 (0.3)**	**0**	**12 (1.2)**	ns
	N. prescriptions	11	1		12	
	Prescription(s) per subject	1.0	1.0		1.0	

[*] only significant *p* values are reported.

% of the doses. However, in a recently published matched case control study using national surveillance systems notification database from 2006 to 2017 in the Apulia region of Italy (Southern Italy) to detect varicella cases by type of vaccine, the single-dose monovalent was reported to be as effective as the single-dose tetravalent against varicella. [26] Moreover, confounder variables were based on outpatient information. For this, residual confounding might be present.

Data sharing

The data used in this study cannot be made publicly available due to Italian data protection laws. The anonymized datasets generated during and/or analyzed during the current study can be provided on reasonable request from the corresponding author after written approval by the Internal Scientific Committee (info@pedianet.it).

Ethics approval

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements.

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CRediT authorship contribution statement

Elisa Barbieri: Writing – original draft, Visualization, Methodology, Conceptualization. **Silvia Cocchio:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Patrizia Furlan:** Writing – review & editing, Formal analysis, Data curation. **Antonio Scamarcia:** Writing – review & editing, Data curation. **Luigi Cantarutti:** Writing – review & editing, Software, Funding acquisition. **Daniele Dona':** Writing – review & editing, Supervision. **Carlo Giaquinto:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Vincenzo Baldo:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Societa' Servizi Telematici reports financial support was provided by Merck Sharp & Dohme LLC. Elisa Barbieri reports financial support was provided by Ministero dell'Istruzione, universita' e ricerca (MIUR). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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