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RESEARCH ARTICLE

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Effectiveness of Universal Varicella Vaccination after ten years of implementation in Tuscany (Central Italy)

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ABSTRACT

Varicella vaccination is currently recommended in several European countries, including Italy. Tuscany Region introduced Universal Varicella Vaccination (UVV) in 2008, and it was later included in the Italian National Immunization Plan 2017–2019. Recently, it has also been made mandatory in Italy for school attendance. The aim of our study was to assess the effectiveness of the UVV program in preventing varicella cases and related hospitalizations in children born between 2008 and 2017, during the pre-pandemic period (2010–2019) in Tuscany (Central Italy). We applied the screening method to assess varicella vaccine effectiveness (VE) for the first and the second vaccine dose in the birth cohorts targeted by the UVV. We considered the vaccination coverage (VC) at 24 months and at 5–6 y of age, and we verified the vaccination status of each notified or hospitalized case to identify breakthrough varicella cases (BV). We assessed a VE of 84.8% (95%CI:83.5–85.9%) for at least one varicella vaccine dose and 95.7% (95% CI: 93.6–97.1%) for the second dose in preventing notifications. VE in preventing hospitalizations was 98.5% (95% CI: 96.7–99.3%) after one dose and 100% after two doses. The median time interval between the first or second vaccine dose and the onset of varicella was 34 months and 28 months, respectively. Our study demonstrated the excellent vaccine effectiveness profile of the vaccines used over a 10-y period in Tuscany, in preventing notified and hospitalized varicella cases in the target cohorts of children, confirming the health benefits of the UVV in Central Italy.

BRIEF SUMMARY

The effectiveness of Tuscany's Universal Varicella Vaccination program in pre-pandemic period was very high in preventing varicella cases and hospitalizations in children born from 2008 to 2017.

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Introduction

Varicella is an acute infectious disease caused by the varicella zoster virus (VZV), which is spread by air droplets or by contact with vesicle liquid. Varicella has a worldwide distribution and affects mostly children. Despite having, generally, a benign outcome, varicella may sometimes be fatal or have severe complications (i.e., pneumonia and encephalitis) in people >15 y, or <1 y old, immunocompromised and newborns from women who have had a rash close to delivery.[1,2]

Anti-varicella vaccines are highly effective in reducing the incidence and burden of the disease.[3] The first varicella vaccine was developed by Dr Takahashi in Japan in the 1970s, and it was based on the attenuated live varicella zoster virus (VZV) Oka strain.[4] In the USA, before the introduction of universal varicella vaccination, almost 11,000 hospitalizations due varicella occurred each year (~3/1000 cases among healthy children and 8/1000 cases among adults). Thanks to the single-dose vaccination introduced in 1995 into a routine childhood vaccination program, the number of hospitalizations and deaths from varicella dropped by ~70% and ~88%, respectively,[5] in USA. However, following "breakthrough varicella" cases (BV) – defined as a case of infection with wild-type VZV occurring ≥42 d after vaccination – the Advisory

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Committee on Immunization Practices (ACIP) recommended a second vaccine dose for children aged 4–6 y in 2007.[5] Nowadays, anti-varicella vaccines are licensed and commercially available worldwide and may be administered as a monovalent (V) or a quadrivalent vaccine together with measles, mumps and rubella components (MMRV). However, varicella vaccine administration is recommended only in a small number of industrialized countries. As for 2023, the Universal Varicella Vaccination (UVV) program in the EU/EEA (European Union/European Economic Area) is recommended at a national level in some countries: Austria, Cyprus, Finland, Germany, Greece, Hungary, Iceland, Italy, Latvia, Liechtenstein, Luxembourg, Slovenia and Spain,[6–10] and only three countries have introduced compulsory varicella vaccination (Hungary, Italy and Latvia).[10] Some other European countries endorsed nationwide vaccine administration for susceptible teenagers and/or susceptible risk groups only (i.e., healthcare workers).[10] Generally, all European countries follow a two-dose MMRV vaccination schedule, administered around the ages of 12–23 months (first dose) and between 15 months and 13 y (second dose).[10,11] In Italy, the UVV has been at first introduced only in some Italian regions (including Apulia, Basilicata, Calabria, Friuli-Venezia Giulia, Sardinia, Sicily, Tuscany and Veneto) at different stages since 2003, before the introduction at the national level.[12] A consequent overall reduction in incidence and hospitalization rates for varicella was observed.[13] In particular, between 2004 and 2012, a fivefold decrease in incidence rates was observed in the pilot regions that implemented the UVV program, dropping from 2.18 per 100,000 to 0.415 per 100,000.[13] Hospitalizations rates declined by approximately 75% between 2004 and 2012, from 3.8 to 1.0 per 100,000 population in 2012.[13] In 2017, the Italian Ministry of Health recommended the UVV (preferably adopting quadrivalent vaccine formulation) in all regions including it into the National Immunization Plan 2017–2019 and introduced a national law, making varicella vaccination mandatory for school attendance for children born in 2017 and onwards.[14,15] Tuscany was one of the first Italian regions to introduce the UVV program with the quadrivalent vaccine in 2008,[16] before the national recommendation. The national and regional recommended schedule called for a two-dose schedule: the first varicella vaccine dose at the age of 13–15 months and the second one at the age of 5–6 y.[15–17]

To monitor the impact of the UVV program in the regional context, a previous study has been conducted in Tuscany[18] for birth cohorts 2008–2011 in the period 2010–2013 using the screening method.[19] The vaccination coverage (VC) at 24 months of age was 79.8% for the birth cohorts 2008–2011 in Tuscany and the calculated vaccine effectiveness for at least one dose of varicella vaccine reached 90.8% (95%CI:89.5%–92.0%). Moreover, the proportion of breakthrough varicella (BV) cases among notified cases was 26.6% and the median time interval between vaccination and symptom onset for BV cases was 25 months.[18] In order to update and reinforce previous scientific evidence, the current study aimed at assessing the effectiveness of the UVV program in preventing varicella cases and hospitalizations due to varicella in children belonging to the birth cohorts 2008–2017 during the period 2010–2019 in Tuscany, by applying the screening method[19] and considering the vaccination coverage (VC) for the first dose (at 24 months of age) and the second vaccine dose (at 5–6 y of age).

Methods

This retrospective cohort study analyzed varicella notifications and hospitalizations data in Tuscany Region and varicella vaccine effectiveness was calculated by applying the screening method.[19] Figure 1 illustrates data flow of the integrated network for data collection, linkage, and management to assess the effectiveness of the Universal Varicella Vaccination Program in Tuscany. The Figure 1 depicts a diagram with various "boxes" representing databases and involved actors and entities and "arrows" indicating the movement and linkage of data.

Data collection and sources

The Health Prevention Departments of the three Local Health Units (LHUs) of Tuscany (Center, South-East, and North-West) provided varicella notifications through their paper archives and/or digital Infectious Disease Reporting Systems PREMAL (acronym for "PREvenzione delle MALattie infettive" - Digital Reporting System") and SIMI (acronym for "Sistema Informativo Malattie Infettive – Infectious Diseases Information System") (Figure 1). The PREMAL system is the new Italian infectious

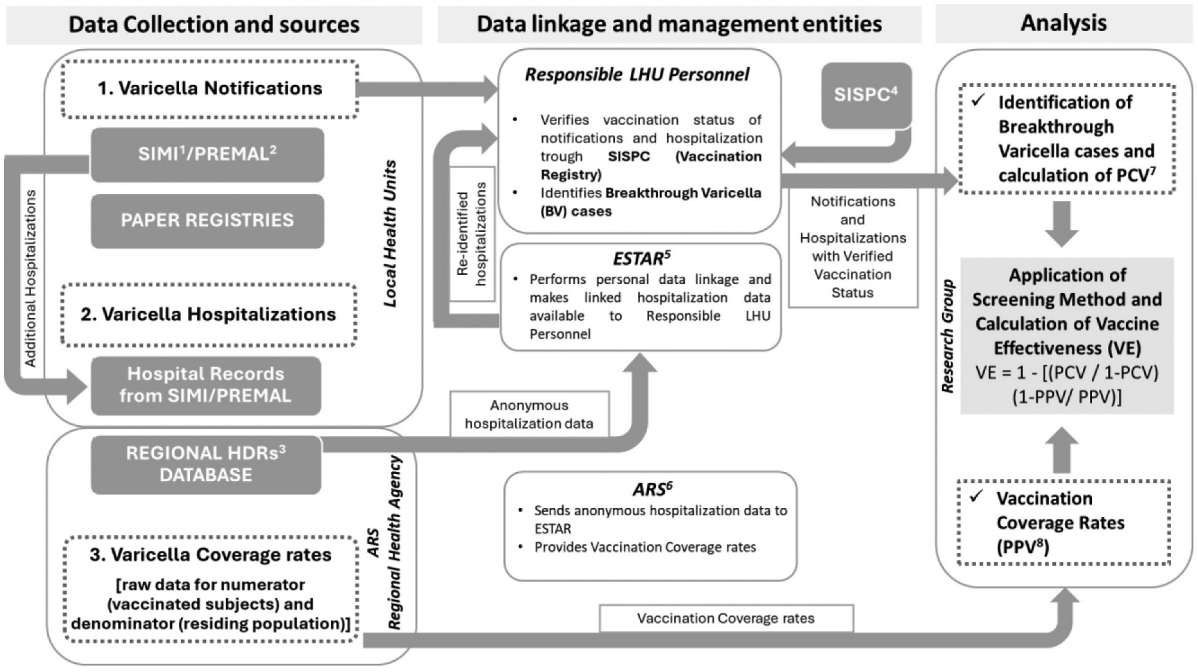

Figure 1. Data flow of the integrated network for data collection, linkage, and management to assess the effectiveness of the Universal Varicella Vaccination Program in Tuscany (Central Italy). Notes: 1. SIMI = Infectious Diseases Information System; 2. PREMAL = PREvenzione delle MALattie infettive – Digital Reporting System; 3. HDRs = Hospital Discharge Records; 4. SISPC = Sistema Informativo Sanitario della Prevenzione Collettiva – Collective Prevention Health Information System; 5. ESTAR = Regional Technical and Administrative Support Agency; 6. ARS = Regional Health Agency of Tuscany; 7. PCV = Proportion of vaccinated subjects among notified/hospitalized cases; 8. PPV = Proportion of Vaccinated Population (Vaccination Coverage).

disease surveillance system for monitoring and reporting confirmed or suspected cases in real time. The Regional Health Agency of Tuscany (ARS) supplied anonymous hospitalization recordings due to varicella from the Hospital Discharge Records (HDRs) regional database. The vaccination coverage (VC) rates at 24 months and at 5–6 y of age were also provided by the Regional Health Agency of Tuscany, which, in addition, supplied raw data of both residing population (denominator) and vaccinated subjects (numerator) for each birth cohort at the regional level. Accountable personnel from the LHUs checked the vaccination status for each known notified/hospitalized varicella case by consulting the SISPC system (acronym for Sistema Informativo Sanitario della Prevenzione Collettiva – Collective Prevention Health Information System) to identify breakthrough varicella (BV) cases. Furthermore, ESTAR (Ente di Supporto Tecnico-Amministrativo Regionale – Regional Technical and Administrative Support Agency) linked personal data (name, surname, date of birth, or Italian fiscal code) to each hospitalization to verify their vaccination status. In particular, ESTAR used the Italian fiscal code to re-identify the hospitalized subjects. Italian fiscal code is a unique alphanumeric code assigned to each individual in Italy, based on their personal details such as name, surname, date of birth, and code corresponding to the place of birth.

Study population, study design and setting

In Tuscany, the Regional Health Service is organized in three macro-areas: Center, South-East and North-West. The study was conducted in all three Tuscany Local Health Units (LHUs) and has included the collection of all notified cases and hospitalizations due to varicella occurring in the study population of children born between 1 January 2008 and 31 December 2017 and residing in Tuscany, between 1 January 2010 and 31 December 2019. We analyzed all notifications reported to the Infectious Disease reporting systems, PREMAL and SIMI, and all the HDRs reported into the HDRs regional database, after the verification of the vaccination status provided by the responsible

LHU personnel. We included in our analyses any hospitalization that had the following ICD9-CM codes in the principal or in the secondary diagnosis: 052.0 (post-varicella encephalitis); 052.1 (varicella hemorrhagic pneumonia); 052.2 (post-varicella myelitis); 052.7 (varicella with other specified complications); 052.8 (varicella with unspecified complications); 052.9 (varicella with no complications).

The following exclusion criteria were applied: place of residence outside Tuscany, date of birth and notification date not included in the birth cohorts under investigation and in the observation period, children who were not old enough to be vaccinated were excluded.

Moreover, records which were duplicates in either notifications or hospitalizations, as well as records with missing data in the vaccination register SISPC or missing fiscal code in the HDR were excluded during the data cleaning procedures.

Screening method application

Varicella VE after at least one dose and after two doses of vaccine was calculated using the screening method proposed by Farrington.[19] Such method is based on the known relationship between the proportion of vaccinated population (PPV = VC = vaccination coverage), vaccine effectiveness (VE) and proportion of vaccinated subjects among notified/hospitalized cases (PCV). Knowing two of these parameters, it is possible to calculate the third. Therefore, reliable values of VC and PCV are essential to obtain a good estimation of VE.[20,21] VE is then given by the following formula: VE = 1 - [(PCV/1-PCV) (1-PPV/PPV)]. The screening method was applied for both individual birth cohorts and the total aggregate of cohorts. As a matter of fact, to obtain the overall VE estimate, the authors aggregated the data related to the total population, vaccinated subjects, notified/hospitalized varicella cases, and breakthrough varicella cases for all birth cohorts included in the analysis (e.g., birth cohorts 2008–2017, for one-dose VE in preventing varicella cases and hospitalizations due to varicella; birth cohorts 2008–2012, for two-dose VE). The VE formula was applied using the aggregated totals of these parameters for each birth cohort but also considering the person-years data as denominator to reflect the total amount of time that all individuals in the population were at risk of developing the disease. Thus, the vaccine effectiveness (VE) values for each cohort and for the total population of the target cohorts of the UVV program (reported in the last row of each table) are calculated summing up the person-years of observation for each cohort as denominator. Specifically, the proportion of the vaccinated population (PPV or VC) and the proportion of vaccinated subjects among notified/hospitalized cases (PCV) for the overall estimate were calculated from the total numbers of cases notified/hospitalized divided by the sum of the person-years of observation across all cohorts. The retrospective cohort study design aimed at reconstructing the entire cohort of cases occurred in vaccinated and in unvaccinated subjects in Tuscany, enabling us to calculate incidence rates in vaccinated and unvaccinated and thus the relative risk for each birth cohort. Indeed, we were able to reconstruct all birth cohorts, observe each cohort for the period corresponding to the person-years of observation, and therefore calculate the incidence rates and the RR.

Moreover, 95% confidence intervals (95% CI) were calculated by birth cohort, expressing VE with the following equation: VE = 1 – (incidence rate vaccinated (Iv)/incidence rate unvaccinated (Iu)).[20,21] The 95% CIs for VE were calculated using the "classical equation of vaccine effectiveness," which is based on the incidence rate ratio. This method was applied for both individual birth cohorts and the overall aggregated estimate.

We also calculated the time interval between the vaccination date and the beginning of symptoms (or disease notification date) for each varicella breakthrough case.

Study approval

The study was approved by the Regional Ethics Committee for Clinical Trials of the Tuscany Region (Section: Paediatric Ethics Committee) on 30 June 2020. Ethics Committee opinion register number: 152/2020. The study was conducted in accordance with the Declaration of Helsinki.

Results

Varicella notifications, hospitalizations due to varicella in Tuscany, vaccination coverage at 24 months and 5–6 y of age

Overall, 3023 cases of varicella have been notified in Tuscany in the period 2010–2019 in the birth cohorts 2008–2017. The median age of the varicella notifications in the whole population was 45 months from a minimum age of 0 to a maximum of 139 months (11 y). The interquartile range of 43 months indicates that the central 50% of children were between 21 and 64 months of age. After the application of the exclusion criteria and following a review and correction of the reporting locations, cases were reassigned to the appropriate Local Health Units (LHUs) based on the actual place of residence. After this adjustment, 2687 cases were retained for analysis and redistributed accordingly among the LHUs. The median age of the varicella notifications in the selected population was 51 months from a minimum age of 15 months to a maximum of 131 months (10 y). The interquartile range of 23 months indicates that the central 50% of children were between 40 and 63 months of age. The selection process of notified varicella cases and hospitalization recordings due to varicella is shown in Figure 2 and in Figure 3, respectively. A total 88 varicella-related hospitalizations were identified from two data sources: the HDR regional database and the SIMI/PREMAL systems. Hospitalized children were between 0 and 9 y old and the median age at the time of admission was 1 y. Four cases were excluded because either their place of residence was outside Tuscany, or LHU personnel were unable to retrieve their fiscal code. After excluding cases with missing or non-Tuscan residence information and removing duplicates reported in both databases, 79 unique hospitalization records were included in the analysis.

The overall varicella vaccination coverage at 24 months of age in the 2008–2017 birth cohorts was 85% in the LHU Center, 75.5% in the LHU North-West, and 79.5% in the LHU South-East. Vaccination coverage rates increased in all three LHUs over time: in the LHU Center, from 78.8% in the 2008 birth cohort to 94.9% in the 2017 birth cohort; in the LHU North-West, from 72.8% to 94.2%; and in the LHU South-East, from 72.6% to 94.5% over the same period.

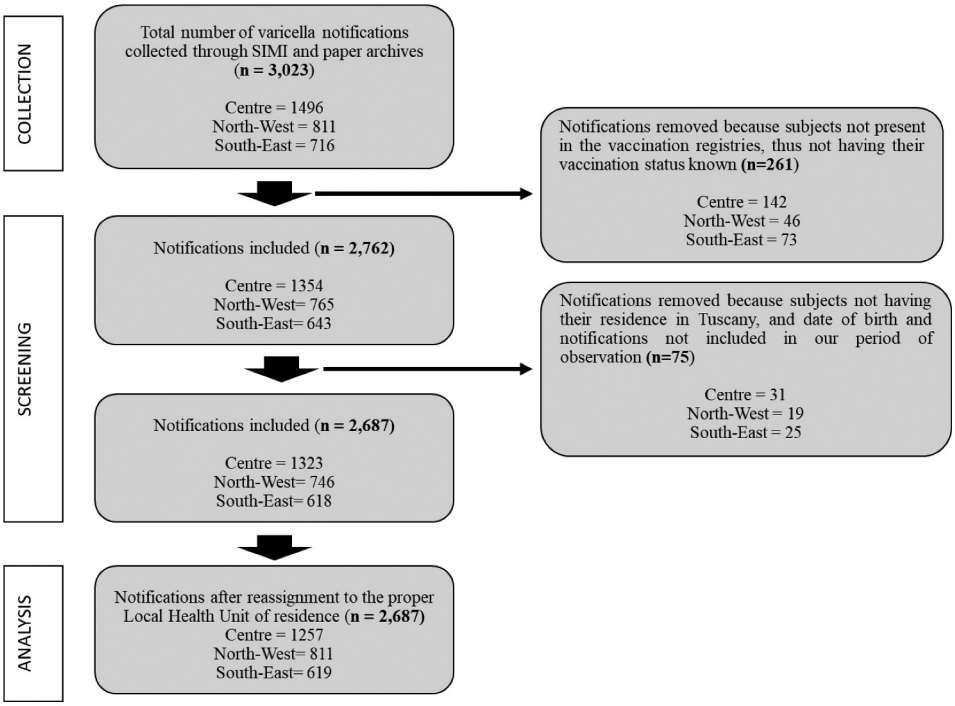

Figure 2. Selection process of notified varicella cases in Tuscany (Central Italy). Note: SIMI = Infectious Disease Information System.

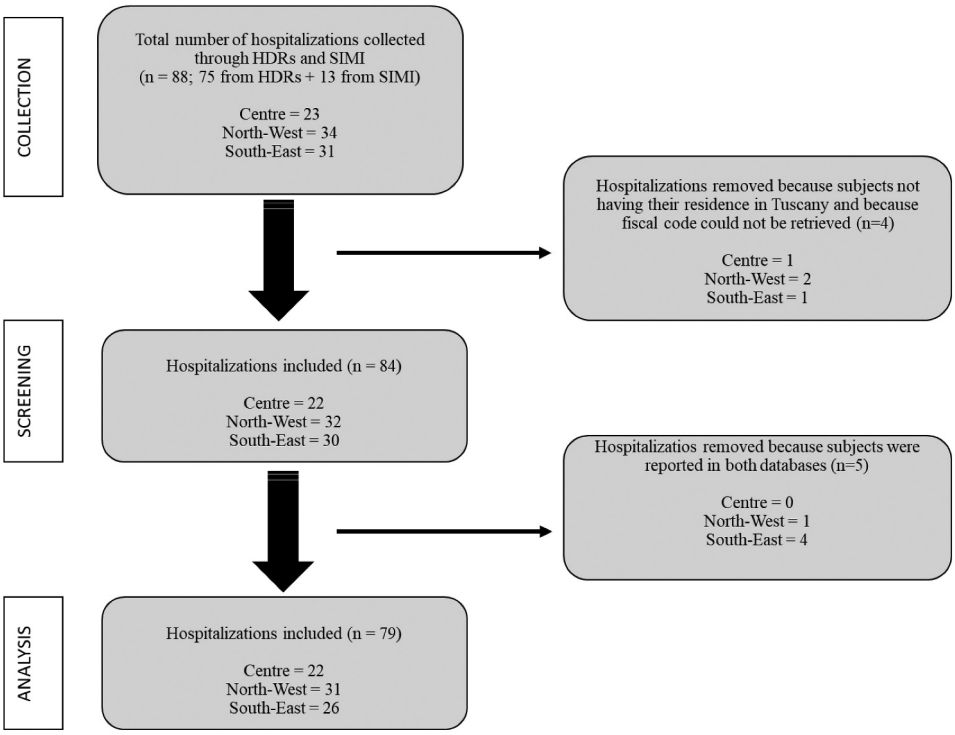

Figure 3. Selection process of hospitalization recordings due to varicella in Tuscany (Central Italy). Notes: HDRs = Hospital Discharge Records; SIMI = Infectious Disease Information System.

Effectiveness of the varicella vaccination program in preventing cases of varicella after at least one dose (VC at 24 months) and after two doses (VC at 5–6 y of age) in Tuscany

After the notification selection and vaccination status verification for each subject, we identified the number of breakthrough varicella (BV) cases. A total of 960 BV cases were identified among individuals who had received at least one vaccine dose (Table 1). Among those vaccinated, 0.41% had a BV: 0.46% in the Centre (510/111, 237), 0.38% in the North-West (272/72,143) and 0.35% in the South-East (178/50,365) LHUs. The highest number of BV cases were reported in the oldest birth cohorts. This is an expected result since older cohorts contribute more "person-time." The overall varicella VE after at least one dose of varicella vaccine (at 24 months of age) in Tuscany was 84.8% (95% CI: 83.5–85.9%). The highest VE was found in the South-

Table 1. Estimated vaccine effectiveness (%) of the UVV after one varicella vaccine dose (at 24 months of age), calculated from the total number of notified varicella cases in the birth cohorts 2008–2017, in the period 2010–2019 in Tuscany.

VARICELLA NOTIFICATIONS AND VACCINATION COVERAGE AT 24 MONTHS*								
Birth cohort	Population (N)	Vaccinated subjects (n)	VC (%)	Notified varicella cases (N_v)	BV cases with at least one vaccine dose (n_{v1})	Percentage of BV cases among notified varicella cases (n_{v1}/N_v) (%)	Vaccine effectiveness (%)	(95% CI)
2008	33,541	25,310	75.5	547	286	52.3	64.4	(57.9–69.8)
2009	32,797	26,964	82.2	453	182	40.2	85.5	(82.5–87.9)
2010	32,464	24,516	75.5	408	129	31.6	85.0	(81.5–87.8)
2011	31,210	24,205	77.6	316	107	33.9	85.2	(81.3–88.2)
2012	30,416	23,456	77.1	300	87	29.0	87.9	(84.4–90.5)
2013	28,937	22,631	78.2	253	86	34.0	85.7	(81.4–88.9)
2014	26,805	20,179	75.3	154	42	27.3	87.7	(82.4–91.3)
2015	25,198	21,942	87.1	103	29	28.2	94.2	(91.0–96.2)
2016	23,693	21,111	89.1	80	9	11.3	98.4	(96.9–99.2)
2017	24,772	23,431	94.6	73	3	4.1	99.8	(99.2–99.9)
2008–2017	**289833**	**233745**	**80.6**	**2687**	**960**	**35.7**	**84.8**	**(83.5–85.9)**

Notes: BV = breakthrough varicella case; VC = vaccination coverage.
*"Vaccination Coverage at 24 months of age" pertains to the Vaccination Coverage used for VE calculation, while the analyzed varicella notifications include all cases identified within the study's defined birth cohorts (2008–2017) and observation period (2010–2019).

Table 2. Estimated vaccine effectiveness (%) of the UVV after two varicella vaccine doses (at 5–6 y of age) calculated from the total number of notified varicella cases in the birth cohorts 2008–2012, in the period 2015–2019 in Tuscany.

VARICELLA NOTIFICATIONS AND VACCINATION COVERAGE AT 5–6 Y								
Birth cohort	Population (N)	Vaccinated subjects (n)	VC (%)	Notified varicella cases (N_v)	BV cases with two vaccine doses (n_{v2})	Percentage of BV cases among notified varicella cases (n_{v2}/N_v) (%)	Vaccine effectiveness (%)	(95% CI)
2008	33,214	22,356	67.3	112	17	15.2	91.3	(85.4–94.8)
2009	30,423	22,930	75.4	53	5	9.4	96.6	(91.5–98.6)
2010	31,205	26,098	83.6	44	5	11.4	97.5	(93.6–99.0)
2011	30,537	26,044	85.3	22	1	4.5	99.2	(93.9–99.9)
2012	30,408	25,634	84.3	3	0	0.0	100.0	–
2008–2012	**155787**	**123062**	**79.0**	**234**	**28**	**12.0**	**95.7**	**(93.6–97.1)**

Notes: BV = Breakthrough varicella; VC = Vaccination Coverage.

East LHU (89.6%; 95% CI: 87.6–91.2%), followed by the Center (88.0%; 95% CI: 86.4–89.1%), and lastly by the North-West one (83.7%; 95% CI: 81.0–85.8%).

We then estimated the varicella VE after two varicella vaccine doses (at 5–6 y of age) in the birth cohorts 2008–2012 in the Tuscany region (Table 2). After two varicella doses, we retrieved 28 BV cases in Tuscany: 18 in the Centre, 5 in the North-West and 5 in the South-East LHUs. The overall ratio between total BV cases/vaccinated subjects was 0.02% (28/123,062), divided as follows: 0.03% in the Center (18/55,933), 0.01% in the North-West (5/39,500) and 0.02% in the South-East (5/27,629) LHUs. We found an overall VE after two varicella vaccine doses of 95.7% (95% CI: 93.6–97.1%) for the whole Tuscany Region. The highest value was observed in the birth cohort 2012, having VE at 100% (no BV cases after two doses was observed), while the lowest value, 91.5% (95% CI: 85%–95%) is reported in the birth cohort 2008, the oldest one. The highest VE at 5–6 y of age were found equally in the South-East LHU (97.6%; 95% CI: 94.1–99.1%) and the North-West (97.6%; 95% CI: 94.1–99.0%) and, lastly, the Center one (95.1%; 95% CI: 91.8–97.0%).

Effectiveness of the varicella vaccination program in preventing hospitalizations

Among the 79 hospitalizations due to varicella in Tuscany in the period 2010–2019 in the birth cohorts 2008–2017, only 7 cases have been classified as BV cases (identified considering the hospital admission date) and all of them occurred after a single vaccine dose (Table 3).

The overall VE of the UVV program in preventing hospitalizations due to varicella after at least one vaccine dose (at 24 months of age) was 98.5% (95% CI: 96.7–99.3%), while no cases of varicella-related hospitalization were observed in those fully vaccinated (having received two doses at 5–6 y of age) during the study period (Table 3). The highest value of VE in preventing hospitalizations was observed in the South-East LHU (VE 99%; 95% CI: 92.4–99.9%), followed by

Table 3. Estimated vaccine effectiveness (%) of the UVV after at least one varicella vaccine dose (at 24 months of age) calculated from the total number of hospitalized cases for varicella in the birth cohorts 2008–2017, in the period 2010–2019 in Tuscany.

VARICELLA HOSPITALIZATIONS AND VACCINATION COVERAGE AT 24 MONTHS								
Birth cohort	Population (N)	Vaccinated subjects (n)	VC (%)	Hospitalized varicella cases (N_v)	BV cases with at least one vaccine dose (n_{v1})	Percentage of BV cases among hospitalized varicella cases (n_{v1}/N_v) (%)	Vaccine effectiveness (%)	(95% CI)
2008	33,541	25,310	75.5	9	3	33.3	83.7	(35.0–95.9)
2009	32,797	26,964	82.2	15	0	0.0	100.0	–
2010	32,464	24,516	75.5	17	2	11.8	95.7	(81.1–99.0)
2011	31,210	24,205	77.6	13	0	0.0	100.0	–
2012	30,416	23,456	77.1	10	0	0.0	100.0	–
2013	28,937	22,631	78.2	1	0	0.0	100.0	–
2014	26,805	20,179	75.3	4	1	25.0	89.1	(0–98.9)
2015	25,198	21,942	87.1	6	0	0.0	100.0	–
2016	23,693	21,111	89.1	2	1	50.0	87.8	(0–99.2)
2017	24,772	23,431	94.6	2	0	0.0	100.0	–
2008–2017	**289833**	**233745**	**80.6**	**79**	**7**	**8.9**	**98.5**	**(96.7 – 99.3)**

Notes: BV = Breakthrough varicella; VC = Vaccination Coverage.

the Centre LHU (VE 97.2%; 95% CI: 90.5–99.1%) and the North-West LHU (VE 96.5%; 95% CI: 88.5–99.9%).

Varicella hospitalizations by diagnosis code

Among the 75 hospitalized cases in which the ICD9-CM code was available (through the HDRs regional database), 30/75 (40%) were recorded as "varicella case with no complications"; 10/75 (13.3%) were reported as "varicella case with other specified complications"; one (1.3%) referred to "varicella with unspecified complications" and lastly, one (1.3%) HDR reported a "post-varicella encephalitis." Importantly, the latter was not vaccinated.

Hospitalized BV cases were between 1 and 4 y old (median age was 24 months, from a minimum age of 15 months to a maximum of 54 months) and they received just the first vaccine dose. Among the seven BV cases found, 3/7 reported varicella as their primary diagnosis: two "varicella with other specified complications" and one "varicella with no complications"; and, as secondary diagnosis, one subject reported having bronchopneumonia, one was undergoing a chemotherapeutic treatment because of leukemia, and one did not have any secondary diagnosis. The remaining four BV cases reported having "pharyngotonsillitis," "unspecified knee infectious arthritis," "febrile seizure," and "breathlessness" as their primary diagnosis.

Time interval between last varicella vaccination and symptoms onset of each case of breakthrough varicella

We also calculated the median time (in months) between the vaccination date (first and second vaccine dose) and the notification date (or beginning of symptoms). We found an overall median time of 34 months (range 0–101 months and IQR = 25 months) between the administration of the first vaccine dose and the notification date of each case of varicella case (BV case after at least one vaccine dose). Similarly, we found a median time of 28 months (range 0–69 months) between the administration of the second dose and the notification date (BV case after two vaccine doses). Most cases of varicella after the second dose occurred between 10 and 45 months (IQR = 35 months). Moreover, the median time interval between the last vaccine dose administered (first or second) and the disease notification date was 34 months (range 0–101 months; IQR = 25 months). Most breakthrough varicella cases occurred between 22 and 47 months after the last vaccine dose. Additionally, among the hospitalized children, the median time between the vaccine dose administration and the hospitalization date was 2.5 months.

Discussion

This study aimed at assessing the effectiveness of the UVV program in Tuscany in the period 2010–2019 in the birth cohorts 2008–2017, target of the regional varicella prevention program. We also aimed at calculating the varicella vaccine effectiveness after one or two doses of varicella vaccine. Our study shows an overall varicella VE of 84.8% in preventing varicella disease after one vaccine dose (at 24 months of age) and a VE value of 95.7% after two vaccine doses and after 10 y of implementation of the UVV. We highlighted some differences, yet small, among the three regional LHUs, perhaps reflecting the different VC at 24 months or at 5–6 y of age in the three LHUs, and maybe a different attitude in reporting cases of varicella to the dedicated varicella surveillance system. As expected, the VE of the UVV program after at least one dose of varicella vaccine reached the highest values in the youngest birth cohorts: i.e., VE as 99.8% (95% CI: 99.2–99.9%) in the birth cohort of 2017, while it was 64.4% (95% CI: 57.9%–69.8%) in the birth cohort of 2008, the oldest cohort included in our study, which contributed for more "person-time." Our results are similar to those collected in Veneto Region that reported a varicella VE of 93% (95% CI: 90–95%) after a single dose in children vaccinated with the quadrivalent formulation ProQuad®.[22,23] On the other hand, in Tuscany, the quadrivalent vaccine (MMRV) was the one mainly administered to children throughout the time 2010–2019 in Tuscany; in particular, the Priorix-Tetra® vaccine[24] was given up to November 2017, followed by ProQuad®. Although it was not possible to calculate the varicella effectiveness for the monovalent or the quadrivalent vaccine, due to missing VC data for the two different vaccine formulations in Tuscany, we can report that 87.2% of our sample population (notified cases in vaccinated

subjects) was vaccinated with one quadrivalent vaccine at the first dose and 12.8% with one of the monovalent varicella vaccines.

As a matter of fact, this favorable impact of the UVV program is confirmed by epidemiological data: the incidence of varicella disease has dramatically dropped over the last 10 y, reporting 4000 cases in 2010 and 745 in 2019. Meanwhile, in 2021 and 2022, only 119 and 186 varicella cases, respectively, have been notified in Tuscany (incidence rate 3.2/100,000 and 5.2/100,000, respectively).[25,26] These data are in line with the epidemiological trend described by Bechini et al. 2015 in which the authors show a 10-fold decrease of varicella estimated real incidence over 10-y time: from 6.7/1,000 in 2003 to 1.6/1,000 in 2012.[13] In addition, thanks to the higher VC reached through the UVV program, remarkable reductions in varicella-related hospitalizations were soon observed in those regions which were firstly involved in the program.[27,28] Specifically, in Sicily, varicella notifications dropped by more than 95% (from 5290 cases in 2003 to 207 cases in 2012) and the number of varicella hospitalizations decreased from 238 in 2003 to 38 in 2001.[29] Similarly, in Apulia, varicella notifications were reduced from 7330 to 234 and hospitalizations dropped from 216 to 22 in the period 2004–2012.[30]

This study is an update of a previous investigation in which the same "screening method" was applied in Tuscany Region to the birth cohorts 2008–2011, during the period 2010–2013.[18] Although the VE after at least one varicella vaccine dose found in the current investigation was 84.8% (95% CI: 83.5–85.9%) which is slightly lower than the previous calculated of 90.8% (95% CI: 89.5–92%), we must consider the wider period of observation in the current study: 10 y (2010–2019) versus 4 y in the previous investigation (2010–2013).

Moreover, an added value of the current analysis, is the investigation of the effectiveness of the two-dose varicella vaccination schedule, for the first time in Tuscany. In particular, we calculated an excellent VE value of 95.7% (95% CI: 93.6–97.1%) after two vaccine doses confirming the benefit of the full immunization in reducing the occurrence of breakthrough varicella cases. As a matter of fact, Tuscany reports one of the highest VC for varicella at 5–6 y old in Italy: it was 84.3% in the year 2019 (birth cohort 2012), compared to the national average value of 38.4%.[31] In the Apulia Region, in which the UVV was introduced in 2006, the VE after one dose increased from 49% (in the birth cohort 2006) to 91.1% (in the cohort 2010); moreover, the VE after two doses increased from 28.8% (birth cohort 1997) to 64.8% (birth cohort 2005).[30] In addition, these real-world data confirm the highly effective impact of the UVV in reducing the burden of disease due to varicella predicted by a previous clinical and economic model applied to the Italian population.[32]

Varicella vaccine effectiveness has been widely assessed worldwide. A 2016 meta-analysis reported 81% VE (95% CI: 78%–84%) after one dose and 92% (95% CI: 88%–95%) after two doses.[33] In Taiwan, VE after one vaccine ranged between 82% (95% CI: 81.3–82.6%) and 93.1% (95% CI: 92.7–93.4%) among children born 2003–2006, vaccinated with Varivax® or Varilrix®.[34–36] In China (Changzhou), during the 2017–2022 transition to a two-dose schedule, VE increased from 82.54% (one dose) to 97.91% (two doses). VE notably improved across all subgroups after 2020.[37] In Germany, VE was 71% overall (95% CI: 57–81%), with 62% (95% CI: 43–75%) after one dose, and 94% (95% CI: 75–98%) after two doses.[38] Vaccine type also influenced VE: higher breakthrough varicella risk was seen with one dose of Varilrix® (RR = 2.8) or Priorix-Tetra® (RR = 2.4), compared to one dose of Varivax®. Two doses of Priorix-Tetra® showed lower risk (RR = 0.5).[38] Another German study reported 86.6% VE after one dose and 97.3% VE after two doses at from 2009 to 2014.[39] In Eastern-European (Czech Republic, Lithuania, Poland, and Slovakia), MMRV (Priorix-Tetra®) showed VE between 95.4% and 97.4%, while monovalent Varilrix® ranged between 59.3% and 74%.[40] In Spain, VE in Navarre was 87% (one dose) and 97% (two doses),[41] while Madrid reported 93.1% VE after one dose between 2001 and 2015.[42] More recently, Barbieri et al. performed a population database analysis to estimate the effectiveness of the varicella vaccine in children under 14 y of age in a high vaccination coverage area from 2004 to 2022 in Veneto region (Italy). In Veneto, universal varicella vaccination was introduced in 2007 with a two-dose schedule at 12–15 months and 5–6 y of age, achieving 90% coverage by 2019. This retrospective analysis used Pedianet, a comprehensive database from 73 family pediatricians in the Veneto Region. In line with our findings, the study reported varicella vaccine effectiveness of 83.4% and 94.7% for those vaccinated with one and two doses, respectively.[43]

An Italian case-control study by Fortunato et al. evaluated the effectiveness of the combined MMRV Priorix-Tetra™ vaccine against varicella of all grades in Southern Italy (Apulia region). The effectiveness against varicella of all severity levels was 77% after a single dose and 93% after two doses of Priorix-Tetra™.

For monovalent varicella vaccine, effectiveness was 72% after one dose. The combined effectiveness of any varicella vaccine was 76% after one dose and 94% after two doses.[44]

The current study is one of the few studies assessing the effectiveness of the varicella vaccination in preventing varicella-related hospitalizations in Italy, with remarkable results in terms of VE, which reached 98.5% (95% CI: 96.7–99.3%) after at least one vaccine dose (at 24 months of age); while it was 100% after two doses, since no hospitalization due to varicella was found in subjects fully vaccinated. Our results are in line with the study by Fortunato et al. with a calculated varicella vaccine effectiveness against hospitalization of 96% after a single dose of any varicella vaccine.[44] While the absolute number of cases may vary by cohort due to different observation times, the adopted screening methodology is appropriate and robust for estimating vaccine effectiveness at the program level, as it relies on the proportions of vaccinated individuals in the population and among notified/hospitalized cases, thereby providing a correct interpretation of the program's overall impact.

We can also speculate that the decreasing number of varicella-related hospitalizations and BV cases we have described over the years (2010–2019) (Table 3) is directly associated with saved costs for the Italian National Health System (NHS). Costs due to varicella in a pediatric population are also well documented in the national and international literature.[45,46]

Finally, we also investigated the time interval between the last administered dose of varicella vaccination and the notification date (or, when it was not available, we considered the date of the symptoms onset) of each BV case. We found that the median time interval between the first and the second varicella vaccine dose and varicella disease onset was 34 and 28 months, respectively. These values are similar to what previously found by Tafuri et al., 2014, who reported a time interval between the first varicella vaccination and virus exposure of about 25 months.[47] The lower circulation of the varicella virus in Tuscany Region in the last decade may have reduced the risk of getting infected and could have had an impact on the lengthening of the time between the last vaccine dose received and the disease. We also observed a wide range of variability in the median interval between the second varicella vaccine dose and varicella notifications (IQR = 35 months), suggesting differences in individual immune response or exposure timing. As a matter of fact, varicella notifications in Tuscany have dropped more than four times in the last 10 y.[25] Breakthrough varicella cases can occur up to 101 months later the last vaccine dose, highlighting the importance of long-term surveillance and consideration of booster strategies if needed. Our findings could hypothetically imply that a shorter interval between the two doses of varicella vaccine might contribute to reducing BV cases, boosting the anti-varicella antibody level after the first dose, though this study did not include serological evidence to directly assess antibody levels. Specifically, our data indicate that the median time interval between the first varicella vaccine dose (typically administered at 13–15 months of age according to the national/regional schedule) and the onset of breakthrough varicella was 34 months. This implies that the median age at which breakthrough cases occurred after the first dose was approximately 47–49 months (around 4 y of age). Consequently, a second dose of varicella vaccine given at around 4 y of age could hypothetically prevent about half of BV cases in the birth cohorts included in the analysis, as the median represents the point by which approximately half of BV cases have occurred. However, considering the very low rate of BV cases among all vaccinated children in the analyzed cohorts (0.41%), shortening the time interval between the two doses of vaccine would not be convenient from an organizational point of view, and should be carefully considered to avoid any potential disruption to a well-established vaccination schedule.[18,48]

The biggest challenge for this study performance was the data collection. A critical issue of this study comes from the fragmented and sometimes unavailability of the varicella notifications in Tuscany Region. Some of the LHUs did not provide data in a digital form, yet in a paper form, which generated some issues due to missing information or misunderstandings. Finally, we observed some discrepancies between the two data collection systems of notifications and HDRs.

As a limitation of the study, it should be noted that the screening method, while being a useful and rapid tool for the preliminary assessment of vaccine effectiveness (VE), has intrinsic constraints that may affect the validity of the findings. The accuracy of this method depends on the reliability of the estimates of both vaccination coverage in the population and the proportion of vaccinated individuals among cases. Any bias or inaccuracy in these parameters can lead to distorted VE estimates. Therefore, results obtained using the screening method should be interpreted with caution. Nonetheless, it remains a practical and widely used approach for monitoring VE, especially in the early phases of a vaccination program or in contexts where individual-level data are unavailable. Moreover, while our study focused on overall program effectiveness and aggregated data as appropriate for the screening method, we acknowledge that its application prevents

deeper insights into specific risk factors, for this reason a detailed analysis of risk factors may not be possible. Despite these operational data collection challenges and study method limitations, we believe that the impact on the overall validity of the study's main conclusions, particularly regarding the high vaccine effectiveness (VE), was limited for several reasons: the screening method is robust and tends to be less sensitive to a uniform underestimation of cases, provided that the relative proportion of vaccinated individuals among cases and in the population is accurate. Moreover, our results, which demonstrate excellent vaccine effectiveness, are broadly consistent with vaccine effectiveness estimates reported in international studies.[33–43] This consistency strengthens the validity of our conclusions on vaccine effectiveness, suggesting that data collection challenges did not invalidate our central estimate of effectiveness. Despite the described limitations, our study provides robust and valuable evidence on the effectiveness of the universal varicella vaccination program in Tuscany during the pre-pandemic period.

Conclusions

Our study demonstrated the excellent vaccine effectiveness profile of the universal varicella vaccination program, over a 10-y period in Tuscany, in preventing notified and hospitalized varicella cases in the target cohorts of children after at least one varicella vaccine dose and after two doses. The VE in preventing hospitalization due to varicella were even higher. Furthermore, a two-dose schedule program is confirmed to be effective in preventing severe varicella cases, as none of the hospitalized children had received two vaccine doses, proving health and economic benefits of the UVV in Tuscany during the pre-pandemic period. However, it is of utmost importance keeping high varicella vaccination coverage in order to guarantee and sustain excellent results. Monitoring the effectiveness of the UVV program should be part of the routine investigations carried out at the regional level to better understand the program's impact and to consider possible revisions of the vaccination schedule.

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References

1. WHO. The immunological basis for immunization series. Module 10: varicella-zoster virus. World Health Organization; 2008 [accessed 2025 Feb 10]. https://apps.who.int/iris/bitstream/handle/10665/43906/9789241596770_eng.pdf;jsessionid=B6ACEB7201AE2250969FCA025B6475C9?sequence=1.
2. WHO. Varicella. Vaccine-preventable disease. Surveillance standards. World Health Organization; 2018 [accessed 2025 Feb 10]. https://cdn.who.int/media/docs/default-source/immunization/vpd_surveillance/vpd-surveillance-standards-publication/who-surveillancevaccinepreventable-22-varicella-r2.pdf?sfvrsn=60ab2518_10&download=true.
3. WHO. Varicella and herpes zoster vaccines: WHO position paper, June 2014–recommendations. Vaccine. 2016;34(2):198–199. doi: 10.1016/j.vaccine.2014.07.068. PMID: 26723191.
4. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet. 1974;2(7892):1288–1290. doi: 10.1016/s0140-6736(74)90144-5. PMID: 4139526.
5. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. 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. PMID: 17585291.
6. Kauffmann F, Bechini A, Bonanni P, Casabona G, Wutzler P. Varicella vaccination in Italy and Germany - different routes to success: a systematic review. Expert Rev Vaccines. 2020;19(9):843–869. doi: 10.1080/14760584.2020.1825947. PMID: 32969747.
7. Spoulou V, Alain S, Gabutti G, Giaquinto C, Liese J, Martinon-Torres F, Vesikari T. Implementing universal varicella vaccination in Europe: The path forward. Pediatr Infect Dis J. 2019;38(2):181–188. doi: 10.1097/INF.0000000000002233. PMID: 30408002.
8. Álvarez García FJ, Cilleruelo Ortega MJ, Álvarez Aldeán J, Garcés-Sánchez M, García Sánchez N, Garrote Llanos E, Hernández Merino Á, Iofrío de Arce A, Montesdeoca Melián A, Navarro Gómez ML, et al. en representación del Comité Asesor de Vacunas de la Asociación Española de Pediatría (CAV-AEP). Calendario de vacunaciones de la Asociación Española de Pediatría: recomendaciones 2021 [Immunisation schedule of the Pediatric Spanish Association: 2021 recommendations]. An Pediatr (Engl Ed). 2021;94(1):.e53.1–.e53.10. Spanish. doi: 10.1016/j.anpedi.2020.10.002. PMID: 33419517.
9. European Centre for Disease Prevention and Control. Varicella vaccination in the European Union. Stockholm: ECDC; 2015 [accessed 2025 Feb 10]. https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/Varicella-Guidance-2015.pdf.

10. ECDC. Vaccine scheduler. Varicella: recommended vaccinations. [accessed 2025 Feb 10]. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=11&SelectedCountryIdByDisease=-1#:~:text=2%20doses%20recommended%20at%204,serology%20for%20varicella%20is%20negative.
11. Bonanni P, Breuer J, Gershon A, Gershon M, Hryniewicz W, Papaevangelou V, Rentier B, Rümke H, Sadzot-Delvaux C, Senterre J, et al. Varicella vaccination in Europe - taking the practical approach. BMC Med. 2009;7(1):26. doi: 10.1186/1741-7015-7-26. PMID: 19476611; PMCID: PMC2697173.
12. Ministry of Health. Piano nazionale prevenzione vaccinale 2012–2014 [Italian national immunization plan 2012–2014]. [accessed 2025 Feb 10]. http://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf.
13. Bechini A, Boccalini S, Baldo V, Cocchio S, Castiglia P, Gallo T, Giuffrida S, Locuratolo F, Tafuri S, Martinelli D, et al. Impact of universal vaccination against varicella in Italy. Hum Vaccin Immunother. 2015;11(1):63–71. doi: 10.4161/hv.34311. Epub 2014 Nov 1. PMID: 25483517; PMCID: PMC4514224.
14. Ministry of Health. Conversione in legge, con modificazioni, del decreto-legge 7 giugno 2017, n. 73, recante disposizioni urgenti in materia di prevenzione vaccinale. Legge 31 luglio 2017, n. 119. (G.U. Serie Generale, n.182 del 05 agosto 2017). [accessed 2025 Feb 10]. http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=60201.
15. Ministry of Health. Piano Nazionale Prevenzione Vaccinale 2017–2019 [Italian National Immunization Plan 2017–2019]. [accessed 2025 Feb 10]. https://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf.
16. Tuscany Region. Aggiornamento direttive regionali in materia di vaccinazioni. Revoca delibere n. 1249 del 24/11/2003, n. 379 del 7/3/2005 e n. 1060 del 10/10/2000. Modifica delibera n. 1386 del 17/12/2001. Delibera n. 1020 27/12/2007. [accessed 2025 Feb 10]. https://www.regione.toscana.it/documents/10180/23315/Delibera%20Gr%201020_2007/ff3dae14-4f5d-464f-a877-4a514d2130c5.
17. Tuscany Region. Calendario vaccinale della regione Toscana. Aggiornamento al 2010. [accessed 2025 Feb 10]. https://www.regione.toscana.it/documents/10180/23315/Calendario%20vaccinale/57a571b1-63e1-4dd0-8060-47bbafdb3d75#:~:text=Dal%20luglio%202008%20la%20vaccinazione,seconda%20con%20vaccino%20DTPa%2FIPV.
18. Pieri L, Porchia BR, Pieralli F, Varone O, Niccolai G, Roselli A, Boccalini S, Bonanni P, Bechini A, Working Group of Tuscan LHU's; Working Group of Tuscan LHU's. Assessment of the effectiveness of the universal varicella vaccination program in Toscana (Italy), in the period 2010-2013. Epidemiol Prev. 2015;39(4 Suppl 1):119–123. PMID: 26499428.
19. Pieri L, Porchia BR, Pieralli F, Varone O, Niccolai G, Roselli A, Boccalini S, Bonanni P, Bechini A. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol. 1993;22(4):742–746. doi: 10.1093/ije/22.4.742. PMID: 8225751. Reprinted as Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol. 2023;52(1):14-21. doi: 10.1093/ije/dyac207.. PMID: 36326585.
20. Lopalco PL. Assessing vaccines and vaccination programmes in the field. IJPH. 2009;6(3):189–193. doi: 10.2427/5772.
21. Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. Epidemiol Rev. 1996;18(2):99–117. doi: 10.1093/oxfordjournals.epirev.a017931. PMID: 9021306.
22. AIFA. Proquad. Riassunto delle caratteristiche del prodotto. [accessed 2025 Feb 10]. https://medicinali.aifa.gov.it/it/#/it/organizzazione/4815/farmaci/36893/stampati/RCP.
23. Giaquinto C, Gabutti G, Baldo V, Villa M, Tramontan L, Raccanello N, Russo F, Poma C, Scamarcia A, Cantarutti L, et al. Impact of a vaccination programme in children vaccinated with ProQuad, and ProQuad-specific effectiveness against varicella in the Veneto region of Italy. BMC Infect Dis. 2018;18(1):103. doi: 10.1186/s12879-018-3017-9. PMID: 29506477; PMCID: PMC5839017.
24. AIFA. Priorix tetra. Riassunto delle caratteristiche del prodotto. [accessed 2025 Feb 10]. https://medicinali.aifa.gov.it/it/#/it/organizzazione/200/farmaci/38200/stampati/RCP.
25. ARS Toscana. La sorveglianza epidemiologica delle malattie infettive in Toscana Rapporto 2021 (novembre 2022) [Epidemiological surveillance of infectious diseases in Tuscany]. Rapporto 2021 (novembre 2022)] [accessed 2025 Feb 10]. https://www.ars.toscana.it/images/Rapporto_malattie_infettive_2022_def_19-12.pdf .
26. ARS Toscana. La sorveglianza epidemiologicadelle malattie infettive in Toscana. Rapporto 2022 (ottobre 2023) [Epidemiological surveillance of infectious diseases in Tuscany]. Rapporto 2022 (ottobre 2023)] [accessed 2025 Feb 10]. hhttps://www.ars.toscana.it/images/pubblicazioni/Rapporti/2023/Rapporto_malattie_infettive_2022_def.pdf.
27. Ministry of Health. State-regions conference. Gazzetta ufficiale n.86 del 14-04-2005. Supplemento ordinario n. 63 [National immunization plan 2005-2007]. [accessed 2025 Feb 10]. https://www.gazzettaufficiale.it/eli/gu/2005/04/14/86/so/63/sg/pdf.
28. Trucchi C, Gabutti G, Cristina Rota M, Bella A. Burden of varicella in Italy, 2001-2010: analysis of data from multiple sources and assessment of universal vaccination impact in three pilot regions. J Med Microbiol. 2015;64(11):1387–1394. doi: 10.1099/jmm.0.000061. Epub 2015 Mar 26. PMID: 25813818.
29. Amodio E, Tramuto F, Cracchiolo M, Sciuto V, De Donno A, Guido M, Rota MC, Gabutti G, Vitale F. The impact of ten years of infant universal varicella vaccination in Sicily, Italy (2003-2012). Hum Vaccin Immunother. 2015;11(1):236–239. doi: 10.4161/hv.36157. Epub 2014 Nov 1. PMID: 25483542; PMCID: PMC4514146.

30. Tafuri S, Fortunato F, Cappelli MG, Cozza V, Bechini A, Bonanni P, Martinelli D, Prato R. Effectiveness of vaccination against varicella in children under 5 years in Puglia, Italy 2006-2012. Hum Vaccin Immunother. 2015;11(1):214–219. doi: 10.4161/hv.36153. Epub 2014 Nov 1. PMID: 25483538; PMCID: PMC4514359.
31. Ministry of Health. Vaccinazioni dell'età pediatrica. Anno 2019 (coorte di nati 2012) [accessed 2025 Feb 10]. https://www.salute.gov.it/imgs/C_17_bancheDati_38_3_3_file.pdf.
32. Bonanni P, Boccalini S, Bechini A, Banz K. Economic evaluation of varicella vaccination in Italian children and adolescents according to different intervention strategies: the burden of uncomplicated hospitalised cases. Vaccine. 2008;26(44):5619–5626. doi: 10.1016/j.vaccine.2008.07.096. Epub 2008 Aug 22. PMID: 18723062.
33. Marin M, Marti M, Kambhampati A, Jeram SM, Seward JF. Global varicella vaccine effectiveness: a meta-analysis. Pediatrics. 2016;137(3):e20153741. doi: 10.1542/peds.2015-3741. Epub 2016 Feb 16. PMID: 26908671.
34. Cheng HY, Chang LY, Lu CY, Huang LM. Epidemiology of breakthrough varicella after the implementation of a universal varicella vaccination program in Taiwan, 2004-2014. Sci Rep. 2018;8(1):17192. doi: 10.1038/s41598-018-35451-y. PMID: 30464186; PMCID: PMC6249209.
35. AIFA. Varivax. Riassunto delle caratteristiche del prodotto [accessed 2025 May 10]. https://medicinali.aifa.gov.it/it/#/it/dettaglio/0000034383.
36. AIFA. Varilrix. Riassunto delle caratteristiche del prodotto [accessed 2025 May 10]. https://medicinali.aifa.gov.it/it/#/it/dettaglio/0000022409.
37. Xiong S, Han C, Wu D, Mi X, Zhang P, Gao H, Cao G, Yao F, Chen C, Lv X. Effectiveness of a 2-dose varicella vaccination program in Changzhou, China, during the transitional period (2017–2022): a registry-based case-cohort study. BMC Public Health. 2025;25(1):207. doi: 10.1186/s12889-025-21348-9. PMID: 39825294; PMCID: PMC11742781.
38. Spackova M, Wiese-Posselt M, Dehnert M, Matysiak-Klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. Vaccine. 2010;28(3):686–691. doi: 10.1016/j.vaccine.2009.10.086. Epub 2009 Oct 27. Erratum in: Vaccine. 2010;28(21):3754. PMID: 19874924.
39. Siedler A, Rieck T, Tolksdorf K. Strong additional effect of a second varicella vaccine dose in children in Germany, 2009–2014. J Pediatr. 2016;173:202–206.e2. doi: 10.1016/j.jpeds.2016.02.040. Epub 2016 Mar 16. PMID: 26995703.
40. Prymula R, Povey M, Brzostek J, Cabrnochova H, Chlibek R, Czajka H, Leviniene G, Man S, Neamtu M, Pazdiora P, et al. Ten-year follow-up on efficacy, immunogenicity and safety of two doses of a combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: results from five East European countries. Vaccine. 2021;39(19):2643–2651. doi: 10.1016/j.vaccine.2021.03.085. Epub 2021 Apr 12. PMID: 33858718.
41. Cenoz MG, Martínez-Artola V, Guevara M, Ezpeleta C, Barricarte A, Castilla J. Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain. Hum Vaccin Immunother. 2013;9(5):1172–1176. doi: 10.4161/hv.23451. Epub 2013 Jan 16. PMID: 23324571; PMCID: PMC3899156.
42. Latasa P, Gil de Miguel A, Barranco Ordoñez MD, Rodero Garduño I, Sanz Moreno JC, Ordobás Gavín M, Esteban Vasallo M, Garrido-Estepa M, García-Comas L. Effectiveness and impact of a single-dose vaccine against chickenpox in the community of Madrid between 2001 and 2015. Hum Vaccin Immunother. 2018;14(9):2274–2280. doi: 10.1080/21645515.2018.1475813. Epub 2018 Jun 22. PMID: 29771626; PMCID: PMC6183198.
43. Barbieri E, Cocchio S, Furlan P, Scamarcia A, Cantarutti L, Dona' D, Giaquinto C, Baldo V. A population database analysis to estimate the varicella vaccine effectiveness in children <14 years in a high vaccination coverage area from 2004 to 2022. Vaccine. 2024;42(26):126387. doi: 10.1016/j.vaccine.2024.126387. Epub 2024 Sep 26. PMID: 39332238.
44. Fortunato F, Musco A, Iannelli G, Meola M, Luigi Lopalco P, Martinelli D. Effectiveness of the combined mmrv Priorix-Tetra™ vaccine against varicella in a large Italian region: a case-control study. Vaccine. 2024;42(7):1608–1616. doi: 10.1016/j.vaccine.2024.02.002. Epub 2024 Feb 9. PMID: 38341290.
45. Leung J, Broder KR, Marin M. Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic literature review. Expert Rev Vaccines. 2017;16(4):391–400. doi: 10.1080/14760584.2017.1294069. Epub 2017 Feb 28. PMID: 28276305; PMCID: PMC5544348.
46. Bozzola E, Spina G, Marchili MR, Brusco C, Guolo S, Rossetti C, Logrieco G, Pignatelli F, Raponi M, Villani A. Pediatric hospitalization for varicella in an Italian pediatric hospital: how much does it cost? Int J Environ Res Public Health. 2021;18(22):12053. doi: 10.3390/ijerph182212053. PMID: 34831809; PMCID: PMC8617963.
47. Tafuri S, Guerra R, Cappelli MG, Martinelli D, Prato R, Germinario C. Determinants of varicella breakthrough: results of a 2012 case control study. Hum Vaccin Immunother. 2014;10(3):667–670. doi: 10.4161/hv.27382. Epub 2014 Jan 7. PMID: 24398423; PMCID: PMC4130284.
48. Bonanni P, Gershon A, Gershon M, Kulcsár A, Papaevangelou V, Rentier B, Sadzot-Delvaux C, Usonis V, Vesikari T, Weil-Olivier C, et al. Primary versus secondary failure after varicella vaccination: implications for interval between 2 doses. Pediatr Infect Dis J. 2013;32(7):e305–13. doi: 10.1097/INF.0b013e31828b7def. PMID: 23838789; PMCID: PMC5500254.