

# Preparing to introduce the varicella vaccine into the Italian immunisation programme: varicella-related hospitalisations in Tuscany, 2004–2012

S Boccalini<sup>1</sup>, P Bonanni<sup>1</sup>, A Bechini<sup>1</sup>

1. Department of Health Sciences, University of Florence, Florence, Italy

Correspondence: Paolo Bonanni (paolo.bonanni@unifi.it)

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**A universal immunisation programme against varicella in the form of the measles-mumps-rubella-varicella (MMRV) vaccine for toddlers aged 13–15 months was introduced in Tuscany in July 2008. An assessment of the impact of this programme on varicella-related hospitalisations 4 years after its introduction could further support its adoption at a national level. The hospitalisation data were analysed in two periods: pre-vaccination (2004–2007) and vaccination period (2009–2012). The high coverage of the vaccines (84% in 2012) resulted in a significant decline in notifications, from 33,114 (2004–2007) to 13,184 cases (2009–2012), and also of hospitalisations, from 584 (pre-vaccination period) to 325 (vaccination period). The hospitalisation rate was 4.1 per 100,000 (95% confidence intervals (CI): 3.4–4.7) before the introduction of vaccination, which dropped to 2.2 per 100,000 (95% CI: 1.7–2.7) in the vaccination period (hospitalisation risk ratios: 0.54; 95% CI: 0.472–0.619). The reduction was most significant in the youngest age groups. The introduction of universal vaccination has already led to a significant decline in hospitalisations due to varicella after just 4 years of implementation. Hospitalisation rates fell noticeably among younger individuals involved in the vaccination programme. The decrease in hospitalisation rate in the older age groups suggests a possible indirect protection.**

## Introduction

Varicella (chickenpox) is the primary manifestation of infection with the varicella zoster virus (VZV) and is a widespread and highly contagious infectious disease. Today, varicella is recognised as the most common exanthematic disease in children in Italy, with an estimated number of 500,000 new cases each year [1,2]. Seroprevalence studies confirm that VZV infection is still predominantly a paediatric infection in Italy, and that there are no substantial differences between blood samples collected in 1996–1997 and those collected in 2003–2004 [2,3].

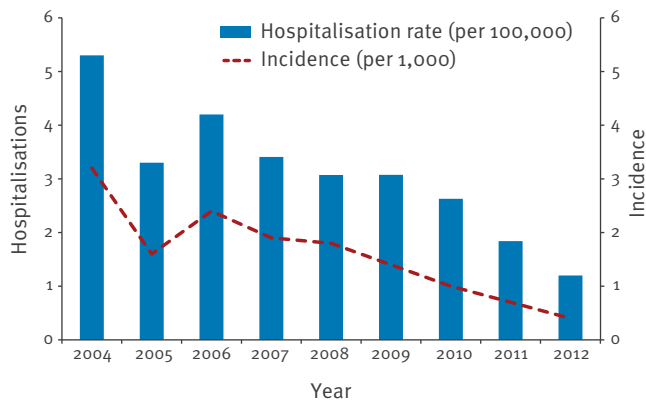
An effective and safe monovalent varicella vaccine has been available in Italy since 1995. However, varicella immunisation has not been widely administered in Italy in the previous decades. In the National Vaccination Plan 2005–2007, the varicella vaccine was recommended only to individuals with a high risk of complications and to susceptible adolescents [4]. However, in order to avoid a shift in the median age of VZV infection towards adulthood, the plan advised introduction of routine childhood varicella vaccination in regions that have been able to achieve and maintain high vaccination coverage against measles, mumps and rubella (MMR) [4]. As a result of these indications, universal immunisation against varicella was not homogeneously implemented at the national level [5,6]. According to an earlier survey of vaccination coverage carried out in Italy by the National Institute of Health (Istituto Superiore di Sanità), the reported childhood vaccination coverage, involving one dose of the varicella vaccine at 24 months of age, was only 17.1% (range: 15.7–18.6%) in Italy in 2008 [7].

In the Italian National Vaccination Plan 2012–2014, (which is the schedule currently being used in 2016) the implementation of universal varicella vaccination at the national level was pushed back until such time when the monitoring and data evaluation of the pilot programmes carried out in some Italian regions (Basilicata, Calabria, the autonomous province of Bolzano, Puglia, Sardinia, Sicily, Tuscany, and Veneto) would be available [8]. Assessment of the epidemiological and economic impact of immunisation against varicella through these regional programmes will enable the rationale for the aforementioned decision to be validated. At the time of publication, the evaluation and related implementation at the national level have not yet been performed.

Tuscany was one of the first Italian regions to introduce and implement a universal vaccination programme

**FIGURE 1**

Hospitalisation rate for varicella diseases and incidence of varicella, Tuscany, Italy, 2004–2012



against varicella with a combined MMRV vaccine for children aged 13–15 months (first dose) and 5 to 6 years (second dose), in July 2008 [9]. The impact of this preventive intervention was evaluated 4 years after the implementation.

In particular, the objective of our study is to evaluate the impact of universal varicella vaccination in Tuscany by analysing all varicella-related hospitalisations reported in the period 2004–2012.

## Methods

The hospital discharge records related to varicella were analysed in order to evaluate the impact of universal varicella vaccination on the hospitalisation rate in Tuscany. Hospitalisation data for 2004–2012 were collected from the Tuscan regional database. In particular, all hospitalised cases for varicella or its complications, as a primary or secondary discharge diagnosis, with the following ICD-9-CM codes (2002 and 2007) were examined: 052.0 (post-varicella encephalitis), 052.1 (varicella (haemorrhagic) pneumonitis), 052.2 (post-varicella myelitis), 052.7 (varicella with other specified complications), 052.8 (varicella with unspecified complication), and 052.9 (varicella without complication) [10].

For each hospitalised case, the collected information included year of hospitalisation, age at time of discharge, sex, region of origin, local health unit, country of residence, hospital days, primary and up to five secondary diagnoses, and total cost of hospitalisation. The costs of hospitalisation correspond to the refunding by the region to the hospitals. Costs are calculated according to the diagnosis-related group (DRG), and also include the possible costs due to the additional days of hospitalisation in excess of the specific outlier threshold. Moreover, the resident population was grouped by age, as retrieved by the Italian National Institute of Statistics database, in order to calculate hospitalisation rates [11].

Hospitalisation data were compared with surveillance data obtained from the Tuscan regional database for varicella cases notified in Tuscany in the same period.

In addition, data on varicella vaccine coverage in children aged 24 months in the period 2008–2012 were included in the analysis. Data on vaccination coverage were also collected from the Tuscan regional database.

Varicella-related hospitalisations were analysed as follows: (i) in the entire period 2004–2012, in order to evaluate the trend over time; (ii) in two periods of 4 years each (the pre-vaccination period, 2004–2007; and the period following the vaccine's introduction, 2009–2012). Data from 2008, the transition year between the two periods mentioned above, were excluded from our analysis. The impact of universal varicella vaccination was assessed by calculating the hospitalisation risk ratios (HRRs) with a 95% confidence interval (CI) (Mantel-Haenszel combined test).

## Results

### Varicella vaccination in Tuscany

Inclusion of the quadrivalent combined MMRV vaccine in the immunisation programme led to rapid achievement of high vaccine coverage against varicella in Tuscany, with a relevant dragging effect. In fact, varicella vaccination with MMRV or monovalent varicella vaccines for children at 24 months of age achieved high coverage soon after implementation: 75.5% in 2010, 82.2% in 2011, and 84.0% in 2012.

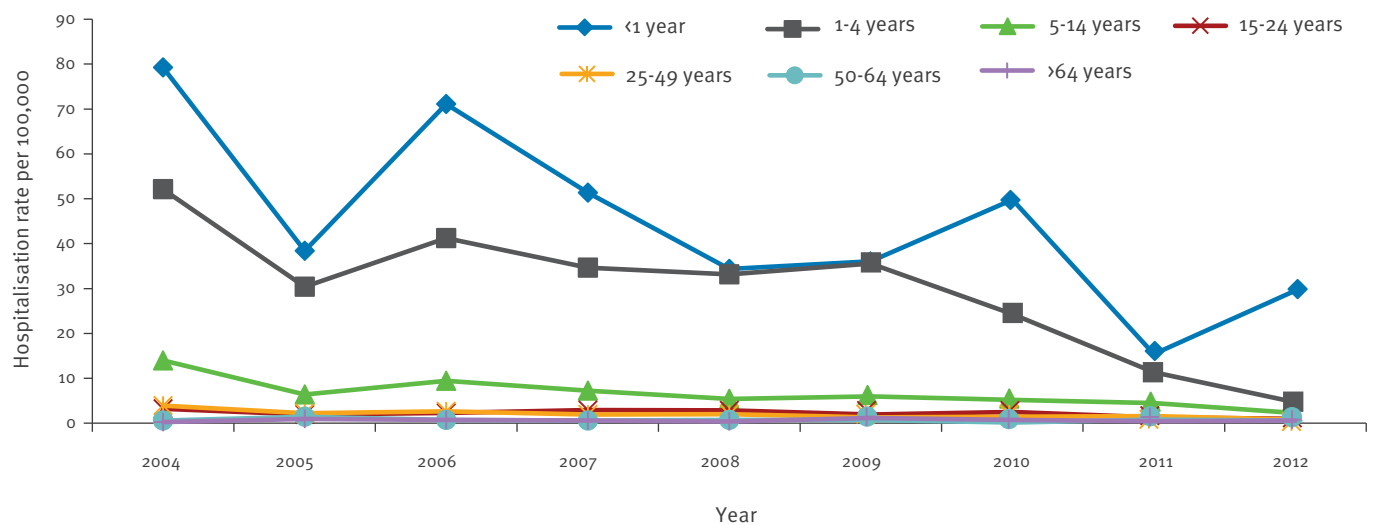
### Varicella cases and hospitalisations

In Tuscany, 52,738 varicella cases were notified to the Regional Health Authority in 2004–2012. A dramatic overall reduction in the number of notifications was reported between 2004 (11,445 cases) and 2012 (1,502 cases). The number of reported varicella cases in the vaccination period (13,184 cases) has been reduced by more than half (60.2% reduction) of that in the pre-vaccination period (33,114 cases). The average incidence rate has declined from 2.30 cases (95% CI: 2.25–2.35) to 0.89 cases (95% CI: 0.86–0.92) per 1,000 inhabitants.

For the same period in 2004–2012, a total of 1,022 hospital discharge records related to varicella or its complications were found in Tuscany. The number of hospitalisations due to varicella diseases showed a decreasing trend over the 9 years analysed: 189 hospitalisations for varicella (5.3 hospitalised cases/100,000 inhabitants; 95% CI: 4.5–6.1) were reported in 2004 and 44 in 2012 (1.2/100,000 inhabitants; 95% CI: 0.8–1.6). In other words, there was a substantial reduction in the number of hospitalisations (by 77%) between 2004 and 2012. The incidence of notified varicella cases and the rate of hospitalised cases for varicella diseases showed the same trend in the period 2004–2012 in Tuscany (Figure 1).

**FIGURE 2**

Hospitalisation rates for varicella, by age group, Tuscany, Italy, 2004–2012



In the pre-vaccination period (2004–2007), there were 584 hospitalised cases related to varicella or its complications in Tuscany, while in the vaccination period (2009–2012) there were 325. A total reduction of 44% (259 fewer cases) in the number of hospitalisations due to varicella was observed between 2009 and 2012. In particular, the average hospitalisation rate for varicella diseases was 4.1 per 100,000 (95% CI: 3.4–4.7) in the period before the introduction of varicella vaccination in Tuscany. This dropped to 2.2 per 100,000 (95% CI: 1.7–2.7) in the vaccination period (HRR: 0.54; 95% CI: 0.47–0.62).

### Hospitalisations for varicella diseases analysed by age at time of discharge

In the period 2004–2012, the hospitalisation rates related to varicella or its complications showed a downward trend in almost all age groups, especially for children under 14 years of age. Children aged between 1 and 4 years, who had historically been affected by varicella diseases and were enrolled in the current universal programme of varicella vaccination in Tuscany, appeared to be the age group that received the greatest benefit from vaccination (a net reduction in hospitalised cases by 90% in the 9-year period, from 60 cases in 2004 to six cases in 2012, corresponding to a hospitalisation rate of 52.1 (95% CI: 38.9–65.3) and 4.6 (95% CI: 0.9–8.4) per 100,000 inhabitants respectively) (Figure 2).

On comparing the pre-vaccination and vaccination period data, the most relevant reduction (>20%) in the rate of hospitalisation due to varicella diseases was again reported in children below 5 years of age (Table).

### Hospital discharge records for varicella diseases analysed by discharge code

The hospital discharge records for primary and secondary diagnoses of varicella or its complications in the study period (2004–2012) were analysed. Among the

1,022 hospitalised cases in Tuscany, a total of 1,041 varicella-related codes (ICD-9-CM) were reported. Of these, 19 hospitalised cases had more than one code identifying varicella diseases in the discharge diagnosis. The most frequently reported discharge code was varicella without complication (052.9). In the period 2004–2012, there were no hospitalisations for post-varicella myelitis (ICD-9-CM 2007 code 052.2).

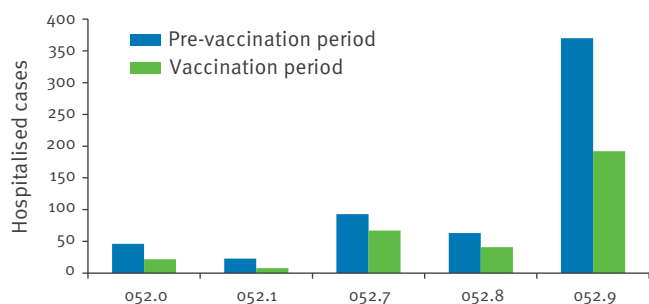
In the switch from the pre-vaccination years (2004–2007) to the vaccination period (2009–2012), a net reduction in hospitalised cases was evident for all discharge codes related to varicella. The greatest reduction in the number of hospitalised cases (178 cases) between the two periods (2004–2007 vs 2009–2012) pertained to the discharge diagnosis of varicella without complications (052.9) (Figure 3). In fact, hospitalisations for this diagnosis decreased by 10.5% in individuals aged 1–14 years who were involved in the vaccination programme.

### Total days of hospitalisation for varicella diseases

In the period 2004–2012, a total of 1,022 patients hospitalised for varicella or its complications in Tuscany remained in the hospital for 6,112 days (an average of six hospital days per patient). The total number of hospital days showed a clear downward trend in the 9 years analysed. In particular, while in 2004 patients were admitted for 960 days in total, in 2012 the total number of hospital days had decreased to 378 days, with an overall reduction of 61% between the first and the last year analysed in the study. In the pre-vaccination period (2004–2007), the total number of days hospitalised was 3,388; this number decreased to 2,021 in the vaccination period (2009–2012), showing a reduction of 40% (1,367 days fewer). The average number of hospital days per patient ranged from 5.8 to 6.6 in the pre-vaccination and vaccination periods.

**FIGURE 3**

Number of hospitalised cases for varicella diseases, by diagnosis code<sup>a</sup>, Tuscany, Italy, in the pre-vaccination (2004–2007) and vaccination periods (2009–2012)

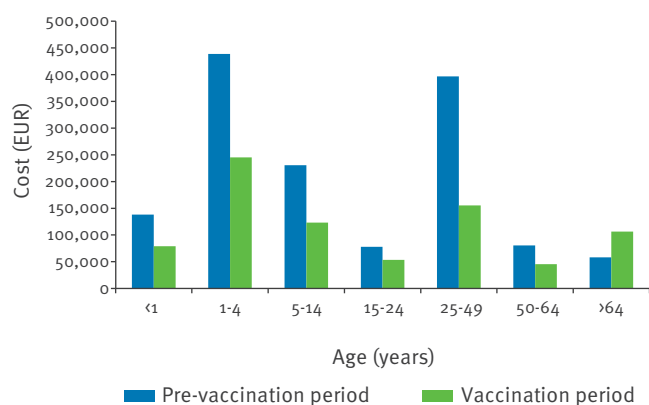


<sup>a</sup> Reference [10].

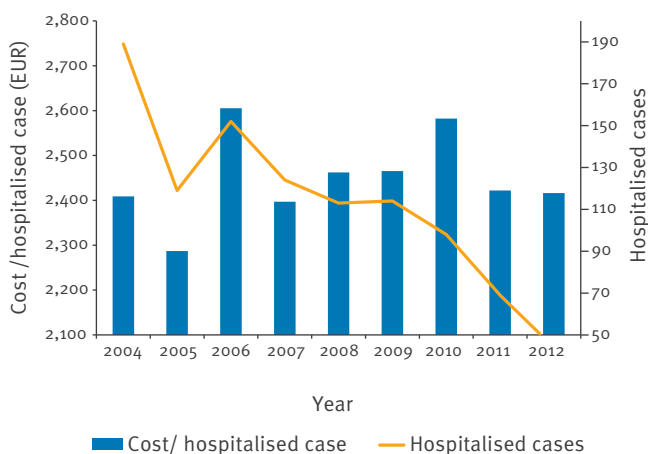
International classification of diseases, ninth revision, clinical modification (ICD-9-CM) codes: 052.0 (post-varicella encephalitis), 052.1 (varicella (haemorrhagic) pneumonitis), 052.2 (postvaricella myelitis), 052.7 (varicella with other specified complications), 052.8 (varicella with unspecified complication), and 052.9 (varicella without complication)

**FIGURE 4**

Total cost of hospitalisation for varicella diseases, by age group, Tuscany, Italy, pre-vaccination (2004–2007) and vaccination periods (2009–2012)

**FIGURE 5**

Cost per hospitalised case for varicella diseases, Tuscany, Italy, 2004–2012



## Cost of hospitalisations due to varicella diseases

In the period 2004–2012, the cost of the 1,022 hospitalisations for varicella or its complications in Tuscany amounted to EUR 2,506,422 (EUR 2,452 per patient on average). The total annual cost of hospitalisation has shown a decreasing trend in the 9 years analysed, similar to the trend in hospitalised cases. In particular, while 189 hospitalisations for varicella occurred in 2004, incurring a cost of EUR 455,267, in the final year of the study 44 patients were hospitalised for a total cost of EUR 106,311, an overall cost reduction of 77%. In the pre-vaccination period (2004–2007) the total cost of hospitalisation due to varicella was EUR 1,420,657 (EUR 355,164/year). In the vaccination period (2009–2012), the cost decreased to EUR 807,535 (EUR 201,884/year). Therefore, hospital costs declined by 43%, creating total savings of EUR 613,121, or EUR 153,280/year.

In the switch from the pre-vaccination period (2004–2007) to the vaccination period (2009–2012), a reduction in the total cost of hospitalisations for varicella diseases was reported in all age groups in Tuscany (Figure 4). However, the cost of hospitalisation increased among individuals over 64 years of age, though the number of hospitalised patients in this age group had not changed much from the pre-vaccination period (21 cases) to the vaccination period (25 cases). This slight increase in costs is mainly attributable to the specific case of an 80-year old patient whose primary diagnosis was pulmonary insufficiency, with secondary diagnoses including generalised convulsive epilepsy, cerebrovascular disease, a kidney disorder, and post-varicella encephalitis. This patient's hospital costs amounted to EUR 34,724. The greatest reduction of hospitalisation costs in absolute number (EUR 241,267) concerns the age group of 25–49 years (data not shown).

In the period 2004–2012, although the number of hospitalised cases and the total annual cost of hospitalisation declined to a great extent, the cost per hospitalised case seemed to show a slight increasing trend over the 9 years analysed (Figure 5). In the pre-vaccination period (2004–2007), the average cost of hospitalised cases was EUR 2,433 per patient, while in the period of varicella vaccination (2009–2012), this cost increased by 2% to EUR 2,485, with an increment of EUR 52 in the average hospitalisation cost of each patient.

## Discussion and conclusions

The routine immunisation of toddlers against varicella has not yet been widely implemented in Europe. Assessment of the epidemiology and disease burden of varicella in each country and evidence for the effectiveness of varicella vaccination could provide support for decision on implementation of routine childhood programmes [12]. Generally, only a small percentage of people infected with varicella diseases are hospitalised in Italy. However, the period 2000–2003 saw an

**TABLE**

Hospitalisations for varicella diseases, by age, and hospitalisation risk ratios with 95% CI, Tuscany, Italy, pre-vaccination (2004–2007) and vaccination periods (2009–2012)

Age group	Pre-vaccination period 2004–2007		Vaccination period 2009–2012		HRR	95% CI
	Hospitalisations	Average rate per 100,000	Hospitalisations	Average rate per 100,000		
<1 year	73	59.6	42	32.7	0.55	0.38–0.80
1–4 years	189	39.5	99	18.9	0.48	0.38–0.61
5–14 years	105	9.2	55	4.5	0.48	0.35–0.67
15–24 years	32	2.6	21	1.7	0.64	0.37–1.19
25–49 years	141	2.7	67	1.3	0.47	0.35–0.63
50–64 years	23	0.8	16	0.5	0.67	0.35–1.26
>64 years	21	0.6	25	0.7	1.14	0.64–2.04
Overall	584	4.1	325	2.2	0.54	0.47–0.62

CI: confidence interval; HRR: hospitalisation risk ratio.

annual average of 1,575 hospitalisations where varicella was the primary diagnosis (1,521 hospitalisations and 54 day-hospital admissions) with a mean hospital stay of 5.3 days per person [2]. Approximately one-third of these cases occurred in people older than 14 years and could have been prevented through a programme of universal vaccination, including an active offer of varicella vaccine to adolescents and adults at high risk without any anamnestic history of varicella diseases [2].

The results of our study show that the introduction of a universal varicella vaccination with MMRV vaccine in Tuscany for all newborns has already resulted in a significant reduction in varicella notifications as well as in the number of hospitalisations due to varicella and related costs, within the first 4 years of implementation. In particular, the current analysis highlights that the number of hospitalised cases has been greatly reduced, especially among younger individuals who were involved in the vaccination programme. However, a positive impact of vaccination on the hospitalisation rate is also evident in other age groups, suggesting a herd immunity effect. Our data on significant reduction of hospitalisation due to varicella in adults are compatible with the results published in Canada [13] and the United States (US) [14] but contradict the hospitalisation data in Germany, where results do not demonstrate herd protection against varicella with 87% vaccination coverage [15]. In addition, the absence of a shift of infection time to the older age groups could be explained by the high vaccination coverage among children. Comparing hospitalisation for uncomplicated varicella (the most frequent discharge diagnosis) in the pre-vaccination period (2004–2007) and in the vaccination period (2009–2012), a clear reduction is evident, thus suggesting that the slight increase in the cost per hospitalised patient might be due to a higher chance that only the most severe cases were hospitalised during the vaccination period.

Limitations of the study are mainly due to the fact that our data on hospitalisations are based on administrative data. A greater appropriateness of hospital admissions during the examined period cannot be excluded as an additional factor in the reduction of hospitalisation rate. Another possible limitation is that varicella may have been coded as zoster or vice versa, even though we included only hospitalisation related to varicella in the analysis. Therefore, the magnitude of the decline implies a marked positive effect of the rapid increase in the vaccination coverage, achieved due to the availability of the quadrivalent MMRV vaccine.

Our study confirms the remarkably favourable clinical impact on notified cases and varicella-related hospitalisations reported in two other Italian regions (Sicily and Veneto), a few years after the implementation of the immunisation programme. Sicily was the first Italian region to offer a universal active vaccination against varicella free of charge to infants at 15 months of age and to all susceptible adolescents at 12 years of age, in January 2003 [16,17].

The Veneto region adopted active and free universal varicella vaccination in January 2005 for children aged 14 months (offering a second dose at the age of 6 years), and a catch-up programme for adolescents aged 12 years. The rapid achievement of high (but not optimal) coverage of vaccination against varicella (78.6% in the 2008 birth cohort) resulted in a net decrement (halving) of the varicella incidence, both in the 0–14 year age group and in the general population, within 4 years of the introduction of the varicella vaccination programme. Furthermore, in this region, hospitalisation due to varicella infection also significantly decreased within 1.5 years of the introduction of the universal varicella vaccination, confirming a significant positive impact of universal varicella vaccination in this Italian region [18–20].

In addition, the reduction in varicella cases and number of related hospitalisations highlighted in Sicily, Veneto, Tuscany, and recently in other Italian regions [21,22],

after the introduction of the universal varicella immunisation programme, had already been observed in other countries. In the US, universal varicella vaccination with one-dose (1996) and two-dose (2006) schedules for children was demonstrated to have a clear and significant impact on the disease burden of VZV infection within a few years of implementation [23-28]. In our recent data, obtained a few years after the start of the varicella immunisation programme, the number of hospitalisations due to varicella shows a trend similar to the results reported in the US [29-35].

A relevant reduction of VZV infections and disease complications has also been observed in Germany, which was the first European country to implement a routine universal vaccination programme against varicella in 2004 [36-38].

From an economic point of view, the universal vaccination of children in Tuscany led to savings amounting to EUR 613,121 over 4 years (EUR 153,280/year), considering only the potential costs of hospitalisations that were prevented by immunisation. In particular, a reduction in hospitalisation costs is evident in all age groups except for individuals over 64 years, where the high cost during the vaccination period can be mainly attributed to the previously described case of a patient aged 80 years who had other medical conditions and incurred hospitalisation costs amounting to EUR 34,724. However, the reported savings could be even more substantial if it is assumed that the real expense is 30–40% higher than the figure calculated through the DRG value, as shown by Azzari et al. [39]. In addition, in our study, we analysed only the cost of hospitalisations due to VZV infection: savings following vaccination would have greatly increased if we also included the other clinical costs and indirect costs due to productivity loss. Therefore, the data we collected in a real-setting scenario seem to confirm the favourable economic contribution of varicella immunisation in Italy, as previously reported in three Italian model-based evaluations [40-42]. Particularly in the mathematic simulation performed by Bonanni et al., a varicella vaccination programme with two doses for toddlers was predicted to lead to reduction by more than 80% in VZV infection and hospitalisation rate in a 30-year time horizon [42]. The results of our study show a 44% reduction in the rate of hospitalisation due to varicella within 4 years of the introduction of varicella vaccination, confirming the model's mathematical forecast.

In conclusion, our experience clearly supports the intention of the Italian health authorities to introduce a national universal routine vaccination against varicella. The use of the quadrivalent MMRV vaccine is a key element to achieving high vaccination coverage in a short period of time, thus speeding up the impact on disease incidence and related hospitalisations. The Italian regional vaccination programmes against varicella may also prove to be a useful example for other

countries where the introduction of routine toddler vaccination is being considered.

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## Conflict of interest

All authors received fees from vaccine producers (GSK, SPMSD, Pfizer, Novartis) for taking part to advisory boards or expert meetings, and grants for acting as investigators (PB) in epidemiological studies co-funded by vaccine producers (Pfizer, GSK).

## Authors' contributions

All the authors contributed equally in the design, collection and analysis of data.

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