

Effectiveness of vaccination against varicella in children under 5 years in Puglia, Italy 2006–2012

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Keywords: Varicella, vaccine effectiveness, screening method, breakthrough, vaccine failure, universal routine vaccination

Abbreviations: 95% CI, 95% Confidence Interval; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; EU/EEA countries, European Union /European Economic Area countries; FDA, U.S. Food and Drug Administration; GIAVA, *Gestione Informatizzata Anagrafe Vaccinale* - Regional Immunization Registry; HRR, Hospitalization Risk Ratio; HDR, Hospital Discharge Registry; ICD9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IRR, Incidence Rate Ratio; MMR, Measles-Mumps-Rubella vaccine; MMR+V, Measles-Mumps-Rubella + Varicella vaccines; MMRV, Measles-Mumps-Rubella-Varicella vaccine; PCV, Proportion of the Cases Vaccinated; PPV, Proportion of the Population Vaccinated; PNPV 2012–2014, Piano Nazionale Prevenzione Vaccinale 2012–2014 - National Immunization Plan 2012–2014; SAGE, Strategic Advisory Group of Experts on Immunization; SIMI, *Sistema informatizzato malattie infettive* - Computerised surveillance system for communicable diseases; STIKO, German Standing Committee on Vaccination; URV, Universal Routine Vaccination; US, United States; VC, Vaccination Coverage; VE, Vaccine Effectiveness; WHO, World Health Organization

In Italy, between 2003 and 2010, 8/21 Regions recommended varicella routine vaccination (URV). The National Immunization Plan (PNPV) 2012–2014 scheduled the introduction of URV nationwide in 2015, following the results achieved by the eight Regions.

Puglia adopted varicella URV in 2006. This study describes epidemiology and costs of varicella in Puglia between 2003 and 2012. One-dose Vaccine Effectiveness (VE) against varicella of any severity and severe hospitalized cases in children was also evaluated.

Vaccination coverage (VC) was estimated from the regional immunization registry. Incidence and hospitalization rates were calculated from computerised surveillance system for communicable diseases and hospital discharge registry (ICD9-CM codes: 052.x), respectively. URV impact was assessed by Incidence Rate Ratios (IRRs) and Hospitalization Risk Ratios (HRRs). Hospitalization costs were also evaluated. VE was estimated using the screening method, where PPV was VC in children aged <72 months and PCV was the proportion of cases vaccinated among notified or hospitalized cases, respectively.

One-dose VC in children aged ≤ 24 months increased from 49% in the birth cohort 2006 to 91.1% in the cohort 2010; 2-dose VC was 64.8% and 28.8% in the 2005 and 1997 cohort, respectively. Comparing pre and post-vaccination era, incidence declined from 122.5 ×100 000 in 2003–2005 to 13.7 in 2009–2012 (IRR = 0.11, 95% CI = 0.10–0.12), hospitalization rate from 3.9 ×100 000 to 1.1 (HRR = 0.29, 95% CI = 0.21–0.4), hospitalization costs from 319 000 Euros/year to 106 000. One-dose VE against varicella of any severity and severe hospitalized disease was 98.8% and 99%, respectively.

Our findings strongly support varicella URV introduction into the Italian *Essential Health Interventions*, as scheduled by 2015.

Background

A live attenuated varicella vaccine was available since 1974.¹ In 1995, the Food and Drug Administration (FDA) licensed the currently used varicella vaccine and in 1996 the Advisory

Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention recommended that children aged 12–18 mo and all susceptible subjects by their 13th birthday should receive one dose of vaccine.²

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Submitted: 06/28/2014; Accepted: 07/12/2014; Published Online: 08/27/2014
<http://dx.doi.org/10.4161/hv.36153>

In the first five years after the introduction of universal routine vaccination (URV) in USA (1996–2001), the overall number of cases and deaths attributable to varicella decreased by 83% and 66%, respectively. In children, the number of deaths declined by 90% and the number of hospitalizations by 88%.³ In Uruguay, where varicella URV was introduced in 1999, the burden of disease decreased substantially since 2005, with an 81% reduction in the proportion of hospitalizations among children and 87% in the incidence of outpatient visits.⁴

Seven studies conducted from 1996 to 2002 in USA showed a vaccine effectiveness (VE) of 71–100% against varicella of any severity and 95–100% against mild and severe disease.^{5–10}

High vaccination coverage (VC) was reached also in other countries, notwithstanding outbreaks of varicella still occurred. In 2002, in UK, an outbreak of varicella was reported in children attending a day-care centre with an attack rate among vaccinees of 48%. VE was 44% against varicella of any severity and 86% against mild or severe disease.¹¹ In 2006, in US, an outbreak occurred in a school where 1-dose VC was 96%, suggesting that the disease remained highly contagious also among vaccinated subjects and that one dose of varicella vaccine could not be sufficient to prevent outbreaks.¹² Findings from these studies encouraged the adoption of routine 2-dose schedule, as subsequently recommended by CDC in 2007.¹³

In the recent “Preliminary guidance on varicella vaccine in the European Union” (2014), ECDC reported how “heterogeneous” were the current recommendations on the vaccination in the EU/EEA countries. Between 2003 and 2010, URV has been recommended in five countries at national level (Germany, Latvia, Greece, Cyprus, Luxemburg) and in two countries at regional level (Spain and Italy); in 17 countries, vaccination is currently recommended only for susceptible teenagers and/or susceptible risk groups.¹⁴ Countries that have implemented URV (i.e.,

Germany, Spain) observed a rapid reduction in the incidence of cases, varicella complications, hospitalization rates and deaths in all age groups, both in vaccinated and unvaccinated individuals. A relative increase in the age of infection has also been reported.^{15–17} ECDC report concluded that more evidences on different aspects of varicella vaccination are needed and recommended countries to assess epidemiological and socioeconomic state, as well as the capacity to achieve high VC for varicella.¹⁴

In Italy, between 2003 and 2010 eight out of 21 regions recommended varicella URV.¹⁸ The National Immunization Plan 2012–2014 has scheduled the introduction of URV at country level in 2015, starting from the birth cohort 2014, in light of the results achieved by the Regions which had already introduced varicella vaccination.¹⁹

A rapid reduction of the incidence of varicella cases was reported in Sicily region where vaccination was introduced in 2003 targeting children in the second year of life.²⁰ A large reduction of both incidence and hospitalization rates was also documented in Veneto region where vaccination is provided to children aged 14 mo with a second dose for 6 y olds and a catch-up dose for 12 y olds since 2005.^{21,22}

In 2006, Puglia region introduced 1-dose varicella URV for children aged 15 mo.²³ In 2009, tetravalent measles-mumps-rubella-varicella vaccine (MMRV) replaced MMR and V vaccines for children aged 13 mo, with a second dose of MMRV or MMR+V at 5–6 or 11–12 y of age.²⁴

In light of the Italian National Vaccination Plan 2012–2014 recommendations and according to ECDC indications,^{14,19} this study aims to describe changes in epidemiology and costs of varicella since the introduction of the vaccination programme in Puglia region. One-dose varicella VE in preventing disease of any severity and severe hospitalized cases in children was also estimated.

Table 1. Vaccination coverage for varicella in children and adolescents (birth cohorts 1996, 1997, 2004, 2005 and 2006–2010), Puglia, Italy

Birth cohort	1-dose VC (%) ≤24 mo of age	2-dose VC (%) 5–6 y of age	2-dose VC (%) 11–12 y of age
1996	-	-	12%††
1997	-	-	28.8%††
2004	-	45.7%†	-
2005	-	64.8%†	-
2006	49%*		
2007	70%*		
2008	75.6%*		
2009	89.7%**		
2010	91.1%**		

*VC for one dose of V vaccine in children aged 15 mo; **CV for one dose of MMRV in children aged 13 mo; †CV for the second dose of MMRV (or MMR+V) at 5–6 y of age; †† CV for the second dose of MMRV (or MMR+V) at 11–12 y of age.

Results

Impact of varicella URV

Vaccination coverage for one dose in children ≤24 mo of age progressively increased from 49% in the birth cohort 2006 to 89.7% and 91.1% in the cohorts 2009 and 2010, respectively (average VC in birth cohort 2006–2010 = 75%). VC for the second dose was 45.7% in the cohort 2004 and 64.8% in the cohort 2005 (5–6 y of age); it was 12% and 28.8% in the cohorts 1996 and 1997, respectively (11–12 y of age; Table 1).

The number of reported cases dramatically decreased from 7330 in 2004 to 234 in 2012 (Fig. 1A). Comparing the pre and post vaccination era, incidence declined from 122.5 × 100 000 (no. of cases = 4953/year) in 2003–2005 to 85.3 × 100 000 (no. of cases = 3474/year; IRR = 0.7, 95% CI = 0.67–0.73) in 2006–2008 and to 13.7 × 100 000 (no. of cases = 560/year; IRR = 0.11, 95% CI = 0.10–0.12) in the 2009–2012 period. In the vaccination era, a significant reduction was recorded in subjects aged <49 y, mainly in the age group 1–4 y (Table 2A).

Hospitalizations for varicella fell from 216 in 2004 to 22 in 2012, similarly to the trend in incidence (Fig. 1B).

Hospitalization rate decreased from $3.9 \times 100\,000$ (no. of cases = 159/year) in 2003–2005 to $2.9 \times 100\,000$ (no. of cases = 118/year; HRR = 0.74, 95% CI = 0.58–0.94) in 2006–2008 and to $1.1 \times 100\,000$ (no. of cases = 47/year; HRR = 0.29, 95% CI = 0.21–0.4) in 2009–2012. In the early vaccination era, a significant decrease was recorded in children 1–4 y old (HRR = 0.71, 95% CI = 0.66–0.76). In the late vaccination era, hospitalization rates significantly declined in children (HRR = 0.16, 95% CI = 0.08–0.33), in the age group 5–14 y (HRR = 0.25, 95% CI = 0.12–0.5) and in young adults (HRR = 0.41, 95% CI = 0.21–0.79; Table 2B).

In the pre-vaccination period, the total costs of hospitalization due to varicella amounted to nearly 319 000 Euro/year. This value progressively decreased in the following years, from nearly 267 000 Euro/year in 2006–2008 to 106 000 Euro/year in 2009–2012, especially in the age group 1–4 y (–78 000 Euro/year), followed by 5–14 y (–55 000 Euro/year), 15–24 y (–21 000 Euro/year) and <1 y (–19 000 Euro/year) age group. A large reduction was also recorded in adults aged 25–49 y (–48 000 Euro/year), whereas a small increase of 4 000 Euro/year occurred in subjects >50 y.

Varicella vaccine effectiveness

PPV in the birth cohorts 2006–2010 was 75%.

From 2006 to 2012, 1178 cases of varicella were notified among children aged <72 mo, 41 of them had received one dose of vaccine ≥ 42 d before the disease onset (PCV = 3.4% -- vaccination failures). One-dose VE against varicella of any severity was 98.8%.

In the 2006–2012 period, 73 children aged <72 mo were hospitalized with a diagnosis of varicella. Two children had received one dose of vaccine ≥ 42 d before the hospital admission (PCV = 2.9% -- vaccination failures). One-dose VE against severe varicella was 99%.

Discussion

A substantial decrease in incidence and hospitalization rates for varicella has been documented in an Italian region that adopted URV since 2006 and reached high VC few years after its introduction. One-dose VE was 98.8% against varicella of any severity and 99% against severe cases.

WHO advocates routine childhood immunization against varicella in countries where high (>80%) and sustained VC can be achieved, since low coverage could theoretically increase the number of cases in older children and adults for whom the disease is more severe.²⁵ In Puglia, VC > 90% has been reached, especially after the introduction of tetravalent MMRV vaccine. The choice of

using a combined vaccine seems to have facilitated the adoption of URV by simplifying vaccine administration, reducing the number of accesses to Vaccination Services and lowering the rate of delayed or missed vaccinations.²⁶ The acceptance of varicella vaccination depending on the use of combined MMRV was recently showed in Germany. A reduction in vaccine uptake was reported after the German Standing Committee on Vaccination (STIKO) recommended concomitant but separate first dose vaccination for MMR and V in September 2011 due to a slightly increased risk of febrile convulsions after first-dose application of combined MMRV.¹⁶

Our findings showed a large impact of varicella URV in Puglia. Incidence declined more than 90% and hospitalization rate >75%, similarly to what happened in USA in the late 1990s and in Germany, Spain and some other Italian regions where URV was introduced in the last decade.^{3,15–18,20–22} Recently, a series of 5 cross-sectional studies performed from 1995 to 2009 in Northern California showed a decline of the incidence of varicella in 5–19-y-olds ranging from 90% to 95% and a reduction of the age-adjusted varicella hospitalization rates in the general

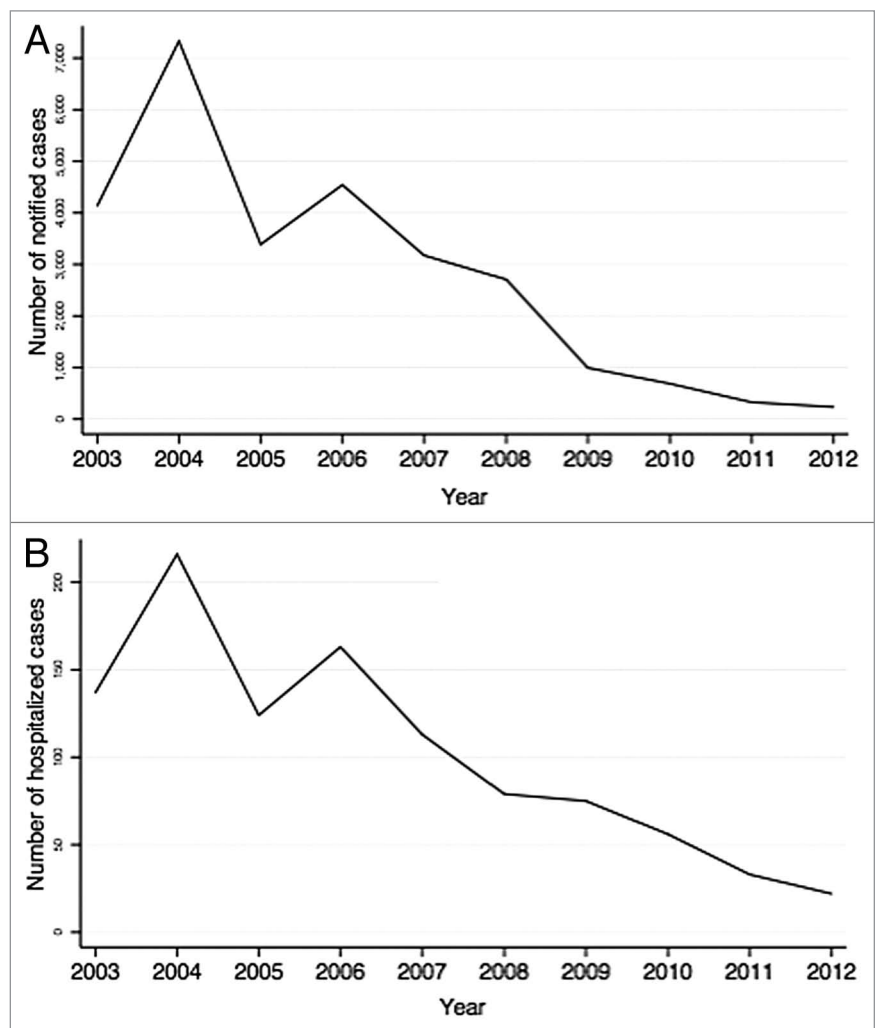


Figure 1. Trends in notified (A) and hospitalized (B) varicella cases. Puglia, Italy, 2003–2012

population of 90%.²⁷ No shift to older age groups was reported, as in our study.

The 1-dose VE for varicella of any severity appears consistent with the finding of 96.8% (95% CI = 96.3–97.2%) reported by Cenoz et al. in Navarra (Spain) in the years 2006–2012.²⁸ A recently published case-control study conducted in the same setting (Navarra, years 2011–2012) among children aged 15 mo to 10 y showed a lower VE: 93% in the first 12 mo after vaccination, 95% between 12 and 35 mo, and 61% after 35 mo (overall VE = 87%, 95% CI = 60–97%). The administration of a second dose helps to re-establish very high levels of effectiveness and to reduce the risk of breakthrough varicella.²⁹ Other previous studies conducted in Puglia between 2009 and 2012 showed lower VE, ranging from 59% to 82%. These studies, performed in close settings, could be influenced by factors such as the proportion of subjects who contracted varicella before the outbreak, the age of subjects and the force of infection.^{30,31} One-dose VE for severe hospitalized disease in our study appears in accordance with data from the last systematic review by WHO SAGE Working Group on Varicella and Herpes Zoster Vaccines,

reporting that a single-dose had an approximate median effectiveness of 95% for preventing moderate or severe disease and 100% for preventing severe disease.³²

Despite the URV impact and effectiveness in countries where it was introduced, some concerns remain about the possible shift in the age at infection or breakthrough varicella cases, but also, to a large extent, about a possible increase of HZ incidence due to the reduction of immunological boosting caused by the varicella vaccination.¹⁴ Our data showed that URV rapidly modified the circulation of the virus in Puglia and no shift in the age at infection was put in evidence.

A significant reduction of cases and hospitalizations was recorded in adults <49 y, with saving of direct costs. Data recently reviewed by Unim B et al. showed that the implementation of varicella URV in all Italian regions by 2015 could save the society from nearly 638 000 Euros (infant strategy) to 53 million annually (combined infant and adolescent strategy).³³

Health economic models also suggest that the introduction of the vaccine may be cost-effective if there is no associated increase in HZ incidence, and may even be cost-saving if indirect societal

Table 2. Incidence rates, IRRs with 95% CIs (A), hospitalization rates, HRRs with 95% CIs (B) of varicella in pre-vaccination era, in one-dose V vaccination era, and in two-doses MMRV vaccination era. Puglia, Italy, 2003–2012

A										
	2003–2005*		2006–2008**				2009–2012***			
Age groups (years)	N	Rate (×100 000)	N	Rate (×100 000)	IRR	95% CI	N	Rate (×100 000)	IRR	95% CI
<1	245	618.4	184	485.7	0.79	0.65–0.95	39	104.4	0.17	0.12–0.24
1–4	2148	1315.2	1479	932.3	0.71	0.66–0.76	161	105.5	0.08	0.07–0.09
5–14	2201	487.1	1570	359.7	0.74	0.69–0.79	289	68.8	0.14	0.12–0.16
15–24	139	26.2	84	16.6	0.63	0.48–0.83	25	5.1	0.19	0.12–0.3
25–49	211	14.2	151	10.1	0.71	0.58–0.88	43	2.9	0.20	0.15–0.29
50–64	6	0.9	4	0.6	0.69	0.20–2.39	2	0.3	0.34	0.07–1.59
>64	4	0.5	2	0.3	0.60	0.12–3.09	1	0.2	0.30	0.04–2.31
Overall	4953	122.5	3474	85.3	0.70	0.67–0.73	560	13.7	0.11	0.10–0.12
B										
	2003–2005*		2006–2008**				2009–2012***			
Age groups (years)	N	Rate (×100 000)	N	Rate (×100 000)	HRR	95%CI	N	Rate (×100 000)	HRR	95%CI
<1	14	35.4	15	39.7	1.12	0.54–2.33	5	12.8	0.36	0.13–1.03
1–4	57	35.1	35	22.3	0.63	0.42–0.97	9	5.6	0.16	0.08–0.33
5–14	42	9.4	29	6.6	0.71	0.44–1.14	10	2.3	0.25	0.12–0.5
15–24	11	2.0	11	2.1	1.05	0.45–2.44	6	1.1	0.57	0.20–1.58
25–49	30	2.0	24	1.6	0.80	0.46–1.36	12	0.8	0.41	0.21–0.79
50–64	2	0.3	2	0.3	0.96	0.15–5.92	3	0.4	1.09	0.19–6.17
>64	2	0.3	2	0.2	0.78	0.1–6.13	3	0.4	1.36	0.22–8.02
Overall	159	3.9	118	2.9	0.74	0.58–0.94	47	1.1	0.29	0.21–0.4

*Pre-vaccination era; **One-dose V vaccination era; ***Two-doses MMRV vaccination era.

costs are included. If the HZ boosting hypothesis is assumed, then models predict a net increase in morbidity and healthcare costs for up to 50 y in some countries, after which net morbidity and healthcare costs will decrease.¹⁴ A recent model by Poletti et al. showed that after varicella immunization an increase of HZ incidence is not a certain fact, rather depends on the force of boosting and which might or not be heavily affected by changes in varicella circulation due to mass immunization.³⁴

A limitation in our study can be related to the analysis of data in the infectious disease surveillance system, commonly affected by low sensitivity and underreporting.³⁵ The methodology we used appears simple and reliable to assess impact and VE against varicella in other regions where URV was adopted. The screening method is a rapid approach for the preliminary assessment of vaccine effectiveness that can be used for monitoring purposes both during the first years after the introduction of a vaccination program and when high coverage levels are reached.³⁶

Our findings strongly support the introduction of routine varicella vaccination into the national list of *Essential Health Interventions*, as scheduled by the National Immunization Plan by 2015.

Methods

Impact of varicella URV

The number of children vaccinated against varicella was obtained from the Regional Immunization Registry (GIAVA). Coverage rates for one dose were estimated in the birth cohorts 2006–2010, for two doses in the birth cohorts 2004–2005 and 1996–1997.

Incidence rates, overall and specific by age, between 2003 and 2012 were calculated by using data collected in the Apulian computerised surveillance system for communicable diseases (referred as SIMI). Hospitalization rates, overall and specific by age, were calculated on data extracted from the regional hospital discharge registry (HDR), selecting all hospital admissions with a main diagnosis of chickenpox or its complications (ICD9-CM codes: 052.x) in the same period.

Both incidence and hospitalization rates before the introduction of URV (calculated as the average annual rate between 2001

and 2005, “pre-vaccination era”) were compared with average rates in 2006–2008 (“1-dose V vaccination era”) and 2009–2012 (“2-doses MMRV vaccination era”) period. The impact of varicella URV was assessed calculating the Incidence Rate Ratios (IIRs) and the Hospitalization Risk Ratios (HRRs) with 95% Confidence Interval (95% CI) by using Poisson regression models. Costs of hospitalization in the examined period were also evaluated.

Varicella vaccine effectiveness

VE against varicella of any severity and severe hospitalized disease in children < 72 mo was estimated using the screening method as follows:

$$VE = \frac{PPV - PCV}{PPV(1 - PCV)}$$

(See ref. 37)

where, PPV (proportion of the population vaccinated) was the average coverage for varicella in the birth cohorts 2006–2010 and PCV was the proportion of cases vaccinated among all notified or hospitalized cases, respectively (the proportion of varicella cases among children adequately vaccinated -- vaccine failures).

Cases notified in the period 2006–2012 were selected from SIMI using the following criteria: age at the onset of symptoms < 72 mo, children residing in Puglia region.

Cases hospitalized in the same period were extracted from HDR following the criteria: age at hospital admission < 72 mo, children residing in Puglia region, main diagnosis of “chickenpox” (ICD9-CM: 052.x).

Cases and hospitalizations were linked with data from GIAVA (linkage key: personal ID number) to classify them as “vaccinated” or “non vaccinated.” A vaccine failure was defined as varicella disease in a child vaccinated \geq 42 d before the date of disease onset or hospital admission.³⁸

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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