INTRODUCTION

Varicella (or chickenpox) is a common and highly contagious exanthematic disease caused by the varicella-zoster virus (VZV). VZV (also known as *Human herpesvirus type 3*) is a member of the family *Herpesviridae* (Hambleton & Gershon, 2005).

In healthy immunocompetent subjects, children in particular, varicella results in mild-to-moderate illness and for this reason, notwithstanding its high morbidity, it is not considered a public health priority.

A greater severity of the clinical picture as well as a higher frequency of complications are seen in immunocompetent susceptible adults, immunosuppressed subjects and newborns to mothers with rash that appears between 5 days before and 2 days after delivery (Heininger & Seward, 2006; Unim *et al.*, 2013).

The complications, which can occur in 2–4 % of cases but that are frequently underestimated, may lead either to a prolonged course of disease or to hospitalization and even death. Infection during pregnancy can result in severe complications in both the mother and the foetus. Pregnant women can develop pneumonia in 10–20 % of
cases, with associated mortality up to 40%. Congenital varicella syndrome, which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring, reaches rates of 2% if maternal infection occurs in the first 20 weeks of pregnancy. The mortality rate is high. Furthermore, severe neonatal infection can follow maternal chickenpox around the time of delivery. In these cases, newborns are at greatest risk of severe or fatal illness, with a mortality rate up to 30% (Enders et al., 1994).

In developed countries, in the absence of extensive immunization, the annual incidence of varicella is assumed to approximate the size of the birth cohort (CDC, 1996; Wharton, 1996; Banz et al., 2003; Gabutti et al., 2008) and to affect almost all children in the course of their childhood (Fairley & Miller, 1996; Marin et al., 2007; Bonanni et al., 2009).

Nowadays, varicella represents the most widespread vaccine-preventable childhood infectious disease in industrialized countries, where many other infections are controlled by national immunization plans (Seward et al., 2002; Banz et al., 2003; Bonanni et al., 2008, 2009; Baldo et al., 2009; Giammanco et al., 2009; Guillaum et al., 2010).

The considerable morbidity in children and severe complications that can occur in adults, with the consequent high burden on healthcare resources, has led several countries outside Europe (Australia, Canada, Costa Rica, Ecuador, Israel, New Zealand, Oman, Panama, Qatar, Saudi Arabia, South Korea, Taiwan, the United Arab Emirates, Uruguay and the USA) to introduce varicella vaccination into the recommended routine childhood national immunization schedule (Marin et al., 2007; Sadzot-Delvaux et al., 2008; Quian et al., 2008; Bonanni et al., 2009; Carrillo-Santistevan & Lopalco, 2014). In Europe, varicella vaccine recommendations are heterogeneous; universal childhood vaccination is recommended at the national level only in five countries (Cyprus, Germany, Greece, Latvia and Luxembourg), and at the regional level in Spain and in Italy (Unim, 2013).

In Italy, the National Vaccination Plan [Piano Nazionale Prevenzione Vaccinale (PNPV)] 2012–2014 reaffirms that varicella vaccine should be provided free of charge to susceptible adolescents (11–18 years of age), women of childbearing age and subjects at high risk. In addition, for the first time, the PNPV 2012–2014 recommends that universal varicella immunization, with a coverage rate >95%, with one dose by 2 years of age and with two doses at 5–6 years should be achieved and maintained, starting from the 2014 birth cohort (Ministero della Salute Italia, 2012).

The Italian Health Service has been decentralized since 2001, and all 21 Italian regions have the responsibility of organizing, delivering and allocating budget for all health services, whilst the State defines the essential health care interventions that all regions have to freely offer to the population. Concerning vaccinations, both mandatory (diphtheria, tetanus, poliomyelitis and hepatitis B) and non-mandatory vaccinations (pertussis, Haemophilus influenzae type b, measles, mumps and rubella) are included in the essential health care interventions, and must by law be provided to all children free of charge across Italy (Alfonsi et al., 2011). Until the approval of the last PNPV in 2012, varicella vaccination was not included amongst immunizations to be offered free of charge to all children, and the regions adopted different varicella vaccination policies.

The purpose of this retrospective study was to assess the burden of varicella in Italy, as recommended by the European Centre for Disease Prevention and Control (ECDC) in its recent guidance Varicella Vaccine in the European Union (ECDC, 2014), evaluating statutory notification data, the National Hospital Discharge Database (NHDD) and mortality data, with a focus on hospitalization and immunization data from three regions that first implemented universal varicella vaccination.

These results may provide baseline data to assess the impact of the universal immunization programme in Italian children that will be implemented starting from the 2014 birth cohort.

METHODS

The following sources of routinely collected surveillance data were analysed: statutory notification data from the Italian Ministry of Health, hospitalization data from the NHDD held by the Italian Ministry of Health and national mortality data from the Italian Institute of Statistics (http://demo.istat.it/).

Statutory notification data. In Italy, varicella is subject to mandatory notification and data are routinely collected from the Italian infectious diseases surveillance system. The only criterion for notification is a clinical diagnosis based on the opinion of the physician examining the patient. Laboratory confirmation is not routinely performed, even though this may lead to underestimation of atypical presentations. National varicella surveillance relies on the reporting by physicians of all suspected cases to local health authorities. The case definition used is clinical. Local health authorities notify the regional health authorities who validate surveillance reports and transmit individual data to the Ministry of Health.

We evaluated varicella cases notified between 1 January 2001 and 31 December 2010.

NHDD data. The Italian NHDD contains anonymized administrative and health data regarding discharged patients, which all public and privately owned hospitals are legally required to report. For each patient, the main discharge diagnosis represents the clinical condition which took up the greatest amount of resources and involved the greatest cost for the hospital. Up to five additional secondary diagnoses may be listed. Diagnoses are coded by using the nomenclature of the International Classification of Diseases – Clinical Modification, 9th edn (ICD9-CM), and transmitted to the region and then to the Ministry of Health, to be included in the regional and national NHDD (Gabutti et al., 2012).

In the present study, the NHDD was retrospectively evaluated for all cases discharged from hospital with both primary and secondary
diagnoses of varicella over the period between 1 January 2001 and 31 December 2010, using the following ICD9-CM codes: 052.0 Post-varicella encephalitis; 052.1 Varicella (haemorrhagic) pneumonitis; 052.2 Post-varicella myelitis; 052.7 Chickenpox with other specified complications; 052.8 Chickenpox with unspecified complication; 052.9 Varicella without mention of complication.

Multiple hospital admissions for the same case were identified by a unique key and excluded from the analysis.

Hospital discharge records with one or more codes for herpes zoster (ICD9-CM: 053.0–053.9) in the main or secondary diagnoses were excluded from the analysis.

**National mortality data.** Varicella mortality data for the years 2001–2003 and 2006–2010 were obtained from the Italian Institute of Statistics database of the causes of mortality (data for the years 2004 and 2005 have never been released at the national level). Causes of death were codified according to the ICD9-CM nomenclature (varicella code 052) for the years 2001 and 2002, and the International Classification of Diseases, 10th edn (code B01) for the years 2003 and 2006–2010.

**Vaccination coverage.** Until the approval of the last PNPV in 2012, varicella vaccine was recommended at the national level only for at-risk groups; therefore, in recent years, the immunization policies for varicella differed widely amongst regions. By 2011, eight regions had adopted a universal varicella vaccination programme targeting children and susceptible adolescents, whilst in the remaining 13 regions, varicella vaccination had been offered free of charge only to risk groups, susceptible adolescents and susceptible women of child-bearing age.

Three regions that were amongst the first to adopt universal vaccination were Sicily, Veneto and Apulia. Sicily introduced a childhood vaccination programme in January 2003; the active and free of charge offer involved children aged 15 months of age and all susceptible adolescents 12 years old. Veneto introduced universal vaccination of children aged 15 months, with a second dose at 6 years of age, and of all susceptible adolescents at 12 years of age in January 2005. Apulia introduced universal routine vaccination against varicella for children aged 14 months through 12 years and two doses for susceptible adolescents and adults in 2006.

**Statistical analysis.** The incidence rates of hospital discharges due to varicella and of statutory notifications and length of stay were calculated by year and age groups. The annual incidence rates per 100 000 population were calculated using as reference the Italian resident population provided by the Italian National Institute of Statistics for the period 2001–2010. The 95% confidence intervals (CIs) were calculated using binomial distribution. Mortality rates were calculated by age group and gender. A linear regression model was used to evaluate the correlation between incidence of varicella hospitalizations or statutory notifications and time. The slope was used to estimate the trend. Statistical analyses were carried out using Stata version 11.2 (Stata).

**RESULTS**

**Statutory notification data**

The mean annual number of cases in Italy in the study period was 88 778 (range: 60 170–126 051) with a mean annual incidence of 150.7 cases per 100 000 population. The annual incidence rate was stable between 2001 and 2003, reached a peak in 2004, with an incidence of 215.6 per 100 000 population, and from 2006, it steadily declined, reaching 102.6 per 100 000 population in 2010 ($β=−9.58; \ P=0.0068$) (Fig. 1).

The differences of incidence rates amongst age groups were statistically significant. The highest incidence rate occurred in the 0–14 years age group (948.6 cases per 100 000 population; 95 % CI: 946.5–950.7), which accounted for 88.8 % of the total cases. The incidence rates were 41.8 (95 % CI: 41.3–42.3), 19.4 (95 % CI: 19.3–19.6) and 1.2 (95 % CI: 1.1–1.2) per 100 000 population in the 15–24, 25–64 and 65+ age groups.

**Fig. 1.** Varicella incidence rate per 100 000 population in Italy: three pilot regions and all other regions, 2001–2010.
> 65 years age group, respectively. Of the total cases, 52 % were observed in males. Incidence rates were significantly higher in males than in females: 161.3 (95 % CI: 160.8–161.7) versus 140.2 (95 % CI: 139.8–140.6) per 100 000 population.

**NHDD data**

Overall, during the period 2001–2010, 20 295 hospitalizations for varicella were observed. The mean annual number of hospitalizations in Italy was 2030 (range: 1482–2553) and the mean annual incidence was 3.4 per 100 000 population, with a decreasing trend very similar to that shown by statutory notifications ($\beta = -0.20; P = 0.0023$). Incidence of hospitalizations reached a maximum of 4.4 per 100 000 in 2004, and a minimum of 2.5 per 100 000 in 2009 and 2010 (Fig. 2).

The highest rate occurred in the 0–14 years age group, notably 47.3 hospitalizations per 100 000 population in children under 1 year of age, 30.8 in the 1–4 years age group and 8.1 in the 5–14 years age group (Table 1).

The overall median length of hospital stay was 4 days, increasing with age (range: 4–10 days); in the elderly > 75 years of age, it was equal to 10 days.

Analysis of data by gender showed that 56.5 % of hospitalized subjects were male, with a male/female ratio of 1.3 : 1.

Of the total hospitalizations due to varicella, 68.4 % involved children (0–14 years age group); 24.9 % were observed in the 15–44 years age group and the remaining 6.7 % in the > 45 years age group.

Hospitalizations due to varicella complications were 33.3 % of the total. Amongst complications requiring hospitalization, 6.4 % were post-varicella encephalitis, 2.6 % varicella (haemorrhagic) pneumonia, 0.05 % post-varicella myelitis, 16.4 % other complications specified and 7.8 % complications not specified. The median length of stay increased from 4 to 5 days when complications were reported, with a range between 4 and 7 days. The age groups 1–4 and > 75 years were those with the highest proportion of complications (38.4 and 39.7 %, respectively).

**National mortality data**

Overall, during 2001–2003 and 2006–2010, 33 deaths due to varicella were reported (eight and 25 deaths in each of the two time periods, respectively), with a mean annual number of four deaths. The mortality rates were found to be consistently higher amongst males than amongst females (24 males and nine females) and higher in the 0–14 and ≥ 65 age groups (0.010 and 0.012 per 100 000 population, respectively).

**Effect of universal vaccination in the three regions considered**

**Hospitalizations.** In Sicily, immunization coverage rates increased from 40.4 % in 2003 to 81.5 % in 2010.

The number of hospitalizations ranged from 238 in 2003, the year of introduction of the vaccination, to 41 in 2010, accounting for hospitalization rates of 4.8 and 0.8 cases per 100 000 population, respectively ($\beta = -0.59; P < 0.0001$).
In Veneto, immunization coverage rates increased from 68.1% in 2006 to 79.4% in 2010. The number of hospitalizations ranged from 150 in 2006, the year of introduction of the vaccination, to 42 in 2010. The hospitalization rate significantly decreased from 3.1 cases per 100 000 in 2006 to 0.9 cases per 100 000 person-years in 2010 ($\beta = -0.35; P < 0.0001$).

In Apulia, immunization coverage rates increased from 43.8% in 2006 to 75.6% in 2010. The number of hospitalizations ranged from 158 in 2006, year of introduction of the vaccination, to 63 in 2010. The hospitalization rate significantly decreased from 3.9 per 100 000 in 2006 to 1.5 cases per 100 000 person-years in 2010 ($\beta = -0.43; P = 0.0004$) (Fig. 3).

### Table 1. Varicella hospitalizations per 100 000 population by age group and year in Italy, 2001–2010

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;1</th>
<th>1–4</th>
<th>5–14</th>
<th>15–24</th>
<th>25–44</th>
<th>45–64</th>
<th>65–74</th>
<th>&gt;75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>52.9</td>
<td>34.9</td>
<td>11.7</td>
<td>2.4</td>
<td>2.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>4.1</td>
</tr>
<tr>
<td>2002</td>
<td>51.2</td>
<td>34.0</td>
<td>12.6</td>
<td>3.3</td>
<td>2.4</td>
<td>0.7</td>
<td>0.5</td>
<td>0.5</td>
<td>4.3</td>
</tr>
<tr>
<td>2003</td>
<td>47.0</td>
<td>29.9</td>
<td>11.0</td>
<td>2.6</td>
<td>2.0</td>
<td>0.5</td>
<td>0.4</td>
<td>0.5</td>
<td>3.7</td>
</tr>
<tr>
<td>2004</td>
<td>58.4</td>
<td>42.8</td>
<td>9.5</td>
<td>2.5</td>
<td>2.6</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>4.4</td>
</tr>
<tr>
<td>2005</td>
<td>38.7</td>
<td>26.4</td>
<td>6.2</td>
<td>2.0</td>
<td>1.9</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>2.9</td>
</tr>
<tr>
<td>2006</td>
<td>56.6</td>
<td>37.6</td>
<td>8.2</td>
<td>2.4</td>
<td>2.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>4.0</td>
</tr>
<tr>
<td>2007</td>
<td>45.3</td>
<td>28.8</td>
<td>6.5</td>
<td>2.1</td>
<td>1.8</td>
<td>0.5</td>
<td>0.4</td>
<td>0.5</td>
<td>3.1</td>
</tr>
<tr>
<td>2008</td>
<td>46.5</td>
<td>29.2</td>
<td>5.7</td>
<td>2.0</td>
<td>1.9</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>3.1</td>
</tr>
<tr>
<td>2009</td>
<td>37.9</td>
<td>22.0</td>
<td>4.9</td>
<td>1.6</td>
<td>1.5</td>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>2010</td>
<td>39.0</td>
<td>23.5</td>
<td>5.0</td>
<td>1.4</td>
<td>1.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>47.3</td>
<td>30.8</td>
<td>8.1</td>
<td>2.2</td>
<td>2.1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Length of stay (days; median)**: 4 4 4 5 5 7 8 10 4

Statutory notifications. The same significantly decreasing trend observed for hospitalizations was reported for statutory notifications in the three regions.

In Sicily, varicella incidence decreased from 105.7 in 2003 to 9.2 per 100 000 population in 2010 ($\beta = -14.44; P < 0.0001$). Similarly, in Veneto, incidence decreased from 225.5 in 2007 to 13.1 per 100 000 population in 2010 ($\beta = -25.78; P = 0.0049$), whilst in Apulia incidence decreased from 121.7 in 2006 to 13.1 per 100 000 population in 2010 ($\beta = -11.39; P = 0.0037$).

Statutory notifications and hospitalization incidence of varicella declined more rapidly in the three regions that...
introduced universal vaccination with respect to the remaining regions (β=−7.28; \( P=0.0428 \) and \( \beta=−0.12; \ P=0.0427 \), respectively) (Figs 1 and 3).

DISCUSSION

A good understanding of the epidemiology of VZV infection is necessary to support the decision of integrating varicella vaccine in the routine immunization schedule and to adequately measure vaccination impact. The assessment of the epidemiological and socioeconomic situation, as well as the capacity to achieve high vaccination coverage levels has been recommended recently by ECDC (2014).

Data from the statutory surveillance system for the years 2001–2010 confirm that varicella is a widespread infectious disease, with a mean of 88 778 cases and a mean annual incidence of 150.7 cases per 100 000 population. Nevertheless, the national incidence rate declined from 215.6 in 2004 to 102.6 per 100 000 inhabitants in 2010. This decreasing national trend might be attributable to the introduction of varicella vaccination in some regional immunization plans.

As expected, the infection is predominantly a paediatric disease (incidence rate 948.6 per 100 000 in the 0–14 years age group), with only 11.2 % of cases affecting people > 15 years old. This trend is consistent with data provided by several studies conducted in other countries in the pre-vaccination era (Halloran et al., 1994; Fairley & Miller, 1996; Brisson et al., 2001).

As highlighted by two previous studies (Ciofi degli Atti et al., 2002; Gabutti et al., 2008), the passive surveillance system is affected by several limitations, such as under-notification, under-diagnosis and notification delays. Consequently, to correctly estimate the burden of the disease, data provided by the national statutory notification system need to be integrated with data from other sources, such as sero-epidemiological studies and active surveillance systems.

In Italy, a Paediatric Sentinel Surveillance System of Vaccine-Preventable Diseases was operational during the 2000–2008. It was an active surveillance system based on a network of paediatricians located throughout Italy and enrolled on a voluntary basis. From 2000 to 2008, ~400 paediatricians participated in the system with a national coverage of 1.7–5 % of children aged 0–14 years. Analysis of varicella data reported to the Paediatric Sentinel Surveillance System of Vaccine-Preventable Diseases showed that the annual incidence rate was four- to sixfold higher than the incidence rate estimated by the statutory notifications. Considering data provided by both surveillance systems, it can be estimated that in Italy ~500 000 cases of varicella occurred each year, which corresponds to the birth cohort (Ciofi degli Atti et al., 2002).

A seroprevalence study conducted in Italy on sera collected from January 2003 to October 2004 (Gabutti et al., 2008) confirmed that varicella is mainly a paediatric disease and that VZV circulation is still widespread, determining natural boosters (Scalia Tomba & Manfredi, 2013; Tafuri et al., 2014). This study also demonstrated a significant risk for VZV infection for pregnant women because of the high percentage of susceptible subjects in the 20–39 years age group.

From 2001 to 2010, the annual hospitalization rate for varicella in Italy was about 3.4 cases per 100 000 population. During the period considered, the highest age-specific incidences of 47.3 and 30.8 per 100 000 resident population was reported in newborns and children 1–4 years of age, respectively, confirming that the majority of the cases occurs in the paediatric population.

Varicella-related hospitalization rates in children differ widely worldwide depending on the geographical region considered and the data collection methodology. The estimates range from 0.82 to 29.2 per 100 000 (Lin & Hadler, 2000; Tseng et al., 2000; Carapetis et al., 2004; Bonhoeffer et al., 2005; Almuneef et al., 2006; Theodoridou et al., 2006; Cameron et al., 2007; Dubos et al., 2007; Grimprel et al., 2007; Liese et al., 2008; Lopez et al., 2011).

As demonstrated in other studies (Brisson et al., 2001; de Melker et al., 2006), both the percentage of hospitalizations amongst varicella cases and mean number of hospital days per admission increase with age. These data confirm the increased severity of varicella and related complications with increasing age. Accordingly, in Italy the highest mortality rates were found amongst children and the elderly (0.010 and 0.012 per 100 000 population, respectively).

These observations combined with the high transmission of VZV in Italy imply that, when vaccination will be introduced in the national immunization programme, vaccination coverage needs to be high to avoid the risk of increased incidence of severe varicella in older age groups and in pregnant women, where VZV infection can have adverse consequences for both the mother and unborn child (de Melker et al., 2006; Gabutti et al., 2008).

Several cost analyses for varicella cases were conducted in Italy and in other European countries. Coudéville et al. (2005) published a study based on diagnosis-related group analysis reporting mean hospitalization costs for a paediatric case of €1187 in France and €3032 in Germany. An Italian study conducted in 2002 by Thiry et al. (2004) evaluated the hospitalization costs with the same methodology and reported a mean cost of about €2196 per paediatric-age patient.

Furthermore, a study conducted in 2007 in Italy demonstrated that the real cost for hospitalization of a paediatric case of varicella was ~30–40 % higher than the cost calculated through the diagnosis-related group analysis value (Azzari et al., 2007), and that costs generated by hospitalization and admissions to Emergency Departments exceeded three-quarters of the total costs that would have been needed to vaccinate an entire birth cohort.
Overall, varicella has a significant impact that can be better addressed by prevention rather than by symptomatic and antiviral treatments (Heininger & Seward, 2006). Prevention through universal vaccination has several advantages, such as reduced complications, decreased health care costs and improved quality of life (Nguyen et al., 2005; Zhou et al., 2008; Blicke et al., 2012).

Safe and effective vaccines against varicella have been licensed for use throughout Europe and the USA. In Europe, two live-attenuated monovalent varicella vaccines and two tetravalent vaccines against measles, mumps, rubella and varicella are available. The epidemiological burden of varicella and the availability of safe and effective vaccines (Grose, 2005) have stimulated an international debate about the suitability of universal vaccination.

The World Health Organization recommends that routine childhood varicella vaccination is considered in countries where the disease is a relatively important public health and socioeconomic problem (WHO, 2014).

At the European level, the European Working Group on Varicella (EuroVar) has recently recommended routine varicella vaccination for all healthy children aged between 12 and 18 months, and for all susceptible children before their 13th birthday, in addition to catch-up for older children and adults who are anamnestically negative for the infection and at high risk of transmission, exposure or complications. However, this policy is recommended only for countries where high vaccination coverage can be rapidly achieved and maintained (Rentier & Gershon, 2004). The EuroVar group stated that this could be reached with a measles, mumps, rubella and varicella combined vaccine. The ECDC has recently reviewed varicella epidemiology in Europe, identifying some knowledge gaps that could influence decisions regarding the implementation of immunization (ECDC, 2014).

In Italy, although eight regions have recently introduced varicella vaccination in their childhood immunization program, chickenpox continues to have an endemo-epidemic trend (Alfonsi et al., 2011). Nevertheless, our data showed that in regions that first introduced a universal immunization programme, coverage rates increased rapidly, with a subsequent decreasing trend in varicella-related hospitalizations and statutory notifications. Notwithstanding, varicella vaccination coverage in children <24 months of age at the national level remains very low.

In conclusion, statutory notifications and hospitalization rates before and after vaccine introduction are important indicators for monitoring the burden of varicella and the impact of immunization policies. Our data confirm that varicella continues to represent a relevant health problem in Italy, where a universal varicella immunization policy is not yet in place. Preliminary data obtained from the three Italian regions that first introduced an extensive vaccination programme demonstrated that universal immunization could significantly reduce the incidence of varicella-related complications and hospitalization rates.

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