RESEARCH ARTICLE

Varicella Admissions in Children and Adolescents in Portugal: 2000–2015

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ABSTRACT

OBJECTIVES: Varicella is a common, usually benign, and autolimited disease in children but can lead to severe complications and hospitalization. With this study, we aim to analyze all varicella hospitalizations to provide epidemiological information to help outline preventive policies.

METHODS: We assessed all varicella hospitalizations in children aged 0 to 17 years, from 2000 to 2015, in mainland, public Portuguese hospitals using a Portuguese administrative database. Seasonality, geographic distribution, severity, complications, risk factors, use of diagnostic and treatment procedures and hospitalization costs were analyzed.

RESULTS: A total of 5120 hospitalizations were registered, with an annual rate of 17.3 hospitalizations per 100 000 inhabitants. A higher number of hospitalizations occurred during the summer period and in Southern regions. The median length of stay was of 4 days (interquartile range: 3.0–7.0). We found a high rate of severe complications, mostly dermatologic (19.6%), neurologic (6.0%), and respiratory (5.1%). Of the total number of patients, 0.8% were immunocompromised and 0.1% were pregnant. Total direct hospitalization costs during the 16-year period were estimated to be 7 110 719€ (8 603 970 USD), with a mean annual cost of 444 419.92€ (537 748.10 USD).

CONCULSIONS: This is the first national study in which useful epidemiological data to evaluate the burden and impact of varicella in Portugal is provided.

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Varicella is usually a benign and self-limited disease, but it represents a significant health burden because it can lead to severe complications requiring hospitalization.[1,2] The main complications associated with varicella are skin and soft tissue infections, including cellulitis and necrotizing fasciitis[3,4]; pneumonia; neurologic complications, such as meningitis, encephalitis, and ataxia; and sepsis.[5]

Without vaccination, ~90% of varicella cases occur in children aged <13 years, particularly in preschool-aged children.[1] The vaccine was created as a strategy to prevent the infection by varicella-zoster virus and its complications.[2,6] Vaccination policies vary among countries, depending on local resources, with an aim to reach a vaccine coverage level of ≥80%, as recommended by the World Health Organization.[7] In Portugal, the 2 live-attenuated vaccines have been available by prescription since 2003 but are not included in the routine National Vaccination Program.

To the best of our knowledge, there is only 1 study in which the incidence of hospitalizations for varicella in Portugal is analyzed by using limited data from 1 hospital.[8] The purpose of our study is to evaluate the hospitalizations related to varicella in children and adolescents in all public Portuguese, mainland hospitals between 2000 and 2015 and assess the main complications, severity, and direct costs, thus generating useful evidence to discuss the introduction of the varicella vaccine in the National Vaccination Program.

METHODS

Study Design

We conducted a retrospective observational study including all patients hospitalized with varicella from 2000 to 2015 using the code 052.X from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). We used an administrative database from mainland, public hospitals, supplied by the Central Administration of the Health System (ACSS), an agency that belongs to the Portuguese National Health System and collects administrative and clinical information through ICD-9-CM codification related to all hospitalizations. Data from the Portuguese National Statistics Institute revealed that almost 72% of all hospitalizations occurring in 2015, in all age groups, were in public hospitals.[9]

We considered only inpatient episodes with a length of stay (LOS) of at least 24 hours and a diagnosis of varicella.

Population data from 2000 to 2015 were considered as available on the Portuguese National Statistics Institute Web site.[10]

Outcome Measures

The main variables of study were the number of hospitalized patients with a diagnosis of varicella and the rate of admissions per age group. As secondary variables, we assessed the seasonality and geographic distribution, severity, risk factors, use of diagnostic tests, required treatment, and direct costs.

Seasonality was assessed by month of hospitalization, and geographic area was evaluated by using the level II of the Nomenclature of Territorial Units for Statistics classification.[11]

Severity was evaluated by the main complications associated with varicella (assessed by using ICD-9-CM codification [Supplemental Table 3]), LOS, in-hospital mortality rate, and use of invasive (96.70, 96.71, and 96.72) or noninvasive ventilation (93.90) as surrogate markers of ICU admission). The risk factors considered were immunodeficiency (042 and 279.X) and pregnancy (V22, V23.83, 647.6). The diagnostic procedures analyzed were chest radiograph (87.44 and 87.49); head computed tomography (CT) scan (87.03); brain MRI (88.91); and blood culture (90.5X). As treatments, we also evaluated the use of intravenous antibiotics (00.14, 99.21, 99.22, E930.9, and 960.X) and intravenous fluid therapy (99.18).

Direct costs were estimated by using a budget allocation model based on diagnosis-related groups through the use of hospital reimbursement tables, corresponding to the year of 2009, provided by the Portuguese Health Service and established by the Portuguese government.[12]

Data Analysis and Statistical Analysis

The population was analyzed according to age and was divided into 7 groups: 0 to 28 days, 29 days to 5 months, 6 to 11 months, <1 year, 1 to 4 years, 5 to 9 years, and 10 to 17 years.

Descriptive analyses were conducted by using IBM SPSS Statistics 24 for Windows (IBM SPSS Statistics, IBM Corporation) and Microsoft Excel 2018. Frequencies and percentages were calculated, taking into account each age group. Continuous variables are presented as mean (SD) or median (interquartile range [IQR]; 25th to 75th percentile), as appropriate. To calculate the rates, we used (as denominator) the population data provided by the National Institute of Statistics.

We conducted a linear regression to assess the admissions trend over time. Categorical variables were compared by using the χ^2 test and the Fisher exact test (comparing mortality and noninvasive and invasive ventilation according to the presence of risk factors). Because LOS did not have a normal distribution, we used the Mann–Whitney U test to compare the LOS according to the presence of risk factors and the Kruskal–Wallis test to compare the LOS according to the age group. P values <.05 were considered statistically significant.

Ethics

The data set was previously anonymized, and its use was authorized by ACSS through a protocol with the Center for Health Technology and Services Research in our university.

RESULTS

During this 16-year period, a total of 5120 hospitalized patients were registered, 3645 of them with varicella as a primary diagnosis. The average number of hospitalizations was 320 per year, providing an annual rate of hospitalizations of 17.3 per 100 000

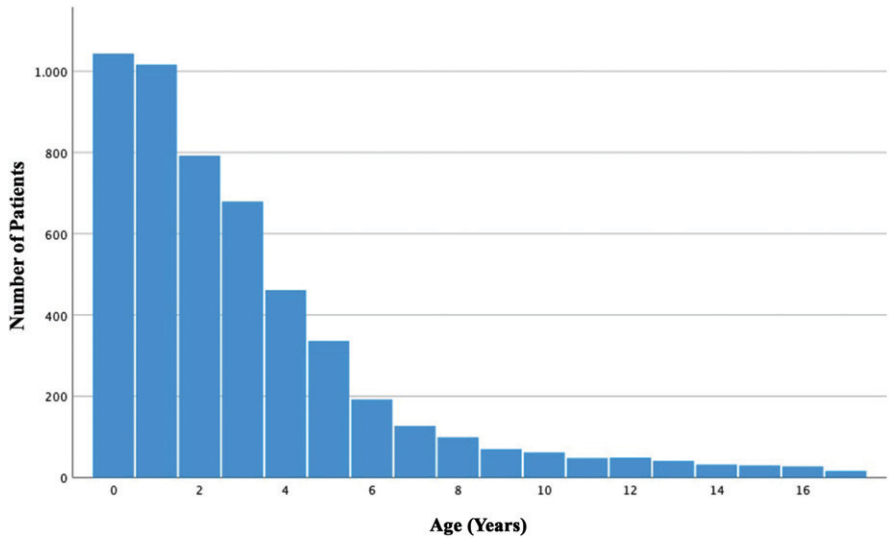

FIGURE 1 Histogram of age distribution.

inhabitants. Children between 1 and 4 years of age accounted for 57.6% of the total admissions, and newborns accounted for 3.7%. A histogram with age distribution is present in Fig 1. The age group between birth and 28 days registered the highest admission rate, at 148.2 per 100 000 inhabitants (Table 1).

Male patients accounted for 54.7% of cases. A visual inspection of Fig 2 indicates that there were 4 peaks of hospitalizations, in 2004, 2007, 2011, and 2014. This said, admissions trends over time were assessed by linear regression, which presented a 95% confidence interval of −4541 to 12 088, so there was no significant variation in the admissions rate along the years. The highest number of admissions occurred in 2007, with 475 admissions. The annual distribution by month revealed a higher number of cases between April and August, mostly during the warmer months (Fig 3). The rate of hospitalizations per 100 000 inhabitants was higher in Southern areas (Alentejo [26.4], Lisbon [21.2], and Algarve [17.2]) than in Central (16.7) and Northern (14.5) regions.

The median LOS was 4.0 days (IQR: 3.0–7.0). The highest LOS was observed for newborns, with a median LOS of 7.0 days, and the lowest for 1 to 4 and 5 to 9 years, with 4.0 days ($P < .001$).

The need for mechanical ventilation was reported in 53 children (1.0%) and noninvasive ventilation was reported in 79% of them. Forty-nine children (0.9%) had the presence of a risk factor, with immunodeficiency in 39 and pregnancy in 6.

TABLE 1 Characteristics of Varicella Admissions in Pediatric Patients, From 2000 to 2015, in Mainland Portugal, by Age Group

	Age Group of Pediatric Patients							
	0 to 28 d	29 d to 5 mo	6 to 11 mo	<1 y	1 to 4 y	5 to 9 y	10 to 17 y	Total
Total hospitalizations, *n* (%)	189 (3.7)	443 (8.6)	411 (8.0)	1043 (20.4)	2948 (57.6)	824 (16.1)	305 (6.0)	5120 (100)
Hospitalization rate (per 100 000)	148.2	69.5	53.7	68.1	46.8	10.2	2.24	17.3
Severity								
LOS, median (IQR)	7.0 (5.0–9.0)	5.0 (3.0–7.0)	4.0 (3.0–6.0)	5.0 (3.0–7.0)	4.0 (2.0–6.0)	4.0 (2.0–7.0)	5.0 (3.0–8.0)	4.0 (3.0–7.0)
Mortality, *n* (%)	0 (0)	1 (0.22)	0 (0)	1 (0.09)	4 (0.14)	2 (0.14)	1 (0.33)	8 (0.15)
Mechanical ventilation, *n* (%)	8 (4.2)	4 (0.9)	7 (1.7)	19 (1.8)	20 (0.7)	9 (1.1)	5 (1.6)	53 (1.0)
Invasive ventilation, *n* (%)	3 (1.6)	0	1 (0.2)	4 (0.5)	4 (0.1)	1 (0.1)	2 (0.6)	11 (0.2)
Noninvasive ventilation, *n* (%)	5 (2.6)	4 (0.9)	6 (1.5)	16 (1.5)	16 (0.5)	8 (1.0)	3 (1.0)	42 (0.8)
Risk groups								
Immunodeficiency, *n* (%)	1 (0.5)	2 (0.5)	1 (0.2)	4 (0.4)	17 (0.6)	12 (1.5)	6 (2.0)	39 (0.8)
Pregnancy, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (2.0)	6 (0.1)
Diagnostic procedures								
Chest radiograph, *n* (%)	16 (8.5)	109 (24.6)	145 (34.5)	270 (25.9)	831 (28.2)	169 (20.5)	77 (25.2)	1347 (26.3)
Head CT scan, *n* (%)	1 (0.5)	6 (1.4)	9 (2.2)	16 (1.5)	126 (4.3)	78 (9.5)	30 (9.8)	250 (4.9)
Brain MRI, *n* (%)	1 (0.5)	4 (0.5)	4 (1.0)	9 (0.6)	51 (1.7)	29 (3.5)	12 (3.9)	101 (2.0)
Blood culture, *n* (%)	125 (66.1)	305 (68.8)	309 (75.2)	739 (70.9)	2258 (76.6)	600 (72.8)	202 (66.2)	3799 (74.2)
Required treatment								
Intravenous antibiotics, *n* (%)	92 (48.7)	210 (47.4)	262 (63.7)	564 (54.1)	1962 (66.6)	475 (57.6)	163 (53.4)	3164 (61.8)
Fluid therapy, *n* (%)	46 (24.3)	171 (38.6)	210 (51.1)	427 (40.9)	1441 (48.9)	416 (50.5)	141 (46.2)	2425 (47.4)

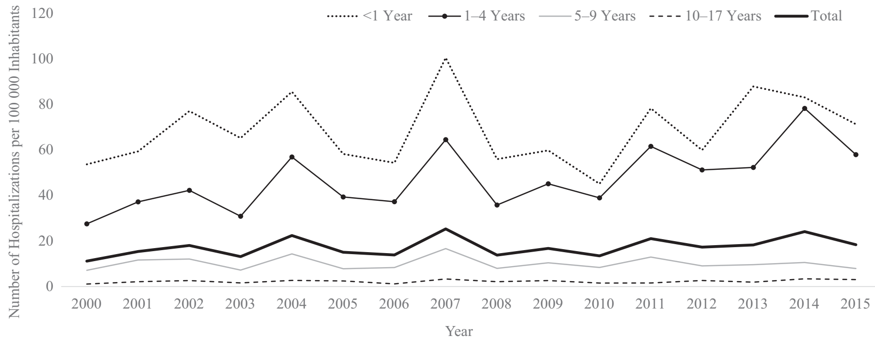

FIGURE 2 Annual variation of varicella-related hospitalizations per 100 000 inhabitants, from 2000 to 2015, for each age group.

The most reported diagnostic procedure was blood culture (74.2%). Chest radiograph, head CT scan, and brain MRI were registered in 26.3%, 4.9% and 2.0% of cases, respectively.

Intravenous antibiotics were reported in 61.8% of the patients and intravenous fluid therapy in 47.4%. The main complications related to varicella are shown in Table 2. The most frequent were skin infections, such as impetigo (10.7%); cellulitis (6.3%); abscess (2.0%); and necrotizing fasciitis (0.5%), followed by respiratory and neurologic disorders, mainly pneumonia (4.4%) and encephalitis (3.6%).

There were 8 deaths during this period (corresponding to 0.15% of the admissions): 3 in children with acute lymphocytic leukemia, 1 with pneumococcal septicemia, 1 with streptococcal septicemia, 1 with *Escherichia coli* infection, 1 with postinfectious intestinal adhesions with obstruction, and 1 with complicated varicella as a first diagnosis.

Individuals with risk factors presented higher mortality rates (2.2% vs 0.1%; $P = .068$) and higher rates of noninvasive (2.2% vs 0.2%; $P = .09$) and invasive ventilation (4.4% vs 0.8%; $P = .05$). The group with risk factors presented a significantly higher median LOS of 7 days, as opposed to 4 days ($P < .001$).

The mean and median estimated costs directly related to the hospitalizations were 1388.80€ (1680.45 USD) and 560.0€ (677.60 USD) (560.0–1355.8) per admission, respectively. Over the 16 years, the estimated mean annual cost was 444 419.92€ (537 748.10 USD), and total costs were estimated to be 7 110 718.70€ (8 603 969.63 USD). The hospitalization of patients with varicella as a primary diagnosis was significantly less costly than that of patients with varicella as a secondary diagnosis, the former costing, on average, 983.48€ (1190.01 USD), whereas the latter cost 2390.46€ (2892.56 USD) ($P < .001$).

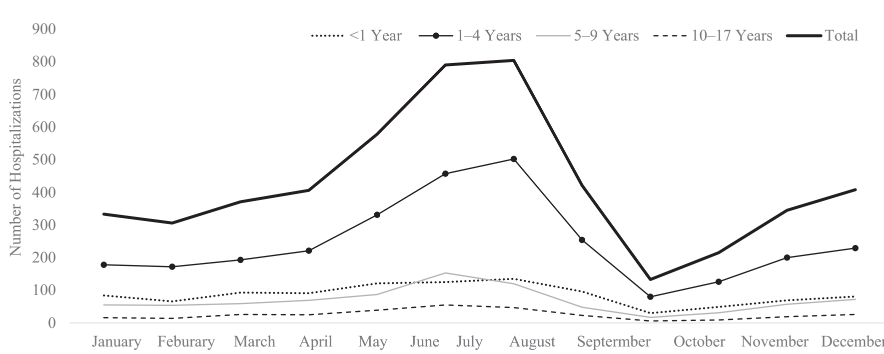

FIGURE 3 Monthly variation of varicella-related hospitalizations, from 2000 to 2015, for each age group.

DISCUSSION

This is the first study in Portugal in which hospitalizations with varicella in children and adolescents in all mainland, public hospitals are assessed, and, therefore, it is important to analyze the impact that varicella has in this country. During these 16 years of study, we registered a total of 5120 hospitalizations, 3645 of which were admitted with a primary diagnosis of varicella. The rate of admissions was 17.3 per 100 000 inhabitants and, as expected, much higher in younger age groups. The age group in which the rate of hospitalizations was highest was newborns (148.2 per 100 000) and progressively decreased as age advanced. This can be explained by the fact that newborns have a significant risk of life-threatening complications in case of perinatal infection and require greater attention and intravenous treatment.[13]

Previous studies from other countries have revealed varying incidence rates of varicella admissions. When comparing our data to the prevaccination era of other countries, we found lower admission rates in Germany (59.4 per 100 000 inhabitants aged <1 year and 3.3 per 100 000 inhabitants of all ages),[14] Italy (50.8 per 100 000 inhabitants aged <1 year and 3.2 per 100 000 inhabitants of all ages),[15] and Denmark (11 per 100 000 inhabitants aged <18 years).[16] Our rate was, however, slightly inferior to the one from Spain (23 per 100 000 inhabitants aged <18 years).[17] Direct comparisons are nonetheless difficult to establish because inclusion criteria, specifically age intervals, were different among studies.

The median LOS was 4 days (IQR: 3.0–7.0), which is also consistent with data from other studies.[16–19] It was higher for neonates and for the ones with risk factors ($P < .001$). Also, adolescents presented a significantly higher IQR. Although adolescents present lower complications rates when compared with

TABLE 2 Incidence of Main Complications Related to Varicella, by Age Group

	Age Group of Pediatric Patients						
	0 to 28 d	29 d to 5 mo	6 to 11 mo	1 to 4 y	5 to 9 y	10 to 17 y	Total
Skin complications, *n* (%)	7 (3.7)	44 (9.9)	95 (23.1)	690 (23.4)	130 (15.8)	34 (11.1)	1000 (19.5)
Abscess, *n* (%)	0 (0)	2 (0.5)	10 (2.4)	76 (2.6)	11 (1.3)	4 (1.3)	103 (2.0)
Cellulitis, *n* (%)	0 (0)	14 (3.2)	29 (7.1)	228 (7.7)	39 (4.7)	12 (3.9)	322 (6.3)
Necrotizing fasciitis, *n* (%)	0 (0)	0 (0)	2 (0.5)	18 (0.6)	7 (0.8)	0 (0)	27 (0.5)
Impetigo, *n* (%)	7 (3.7)	28 (6.3)	54 (13.1)	368 (1.2)	73 (8.9)	18 (5.9)	548 (10.7)
Neurologic complications, *n* (%)	0 (0)	3 (0.7)	10 (2.4)	173 (5.9)	91 (11.0)	28 (9.2)	305 (6.0)
Myelitis, *n* (%)	0 (0)	0 (0)	0 (0)	1 (0.0)	5 (0.6)	0 (0)	6 (0.1)
Encephalitis, *n* (%)	0 (0)	2 (0.5)	2 (0.5)	93 (3.2)	69 (8.4)	19 (6.2)	185 (3.6)
Meningitis, *n* (%)	0 (0)	0 (0)	0 (0)	1 (0.0)	1 (0.1)	1 (0.3)	3 (0.1)
Cerebellar ataxia, *n* (%)	0 (0)	0 (0)	0 (0)	11 (0.4)	7 (0.8)	4 (1.3)	22 (0.4)
Febrile seizures, *n* (%)	0 (0)	1 (0.2)	8 (1.9)	67 (2.3)	9 (1.1)	4 (1.3)	89 (1.7)
Respiratory complications, *n* (%)	3 (1.6)	13 (2.9)	27 (6.6)	168 (5.7)	40 (4.9)	10 (3.3)	261 (5.1)
Acute tonsillitis, *n* (%)	0 (0)	1 (0.2)	1 (0.2)	26 (0.9)	8 (1.0)	1 (0.3)	37 (0.7)
Pneumonia, *n* (%)	3 (1.6)	12 (2.7)	26 (6.3)	142 (4.8)	32 (3.9)	9 (3.0)	224 (4.4)
Osteomuscular complications, *n* (%)	0 (0)	0 (0)	9 (2.2)	47 (1.6)	16 (1.9)	2 (0.7)	74 (1.4)
Mastoiditis, *n* (%)	0 (0)	0 (0)	1 (0.2)	9 (0.3)	2 (0.2)	1 (0.3)	13 (0.3)
Aseptic arthritis, *n* (%)	0 (0)	0 (0)	7 (1.7)	31 (1.1)	12 (1.5)	0 (0)	50 (1.0)
Osteomyelitis, *n* (%)	0 (0)	0 (0)	1 (0.2)	7 (0.2)	2 (0.2)	1 (0.3)	11 (0.2)
Gastrointestinal complications, *n* (%)	0 (0)	6 (1.4)	10 (2.4)	42 (1.4)	8 (1.0)	2 (0.7)	68 (1.3)
Gastroenteritis, *n* (%)	0 (0)	6 (1.4)	10 (2.4)	42 (1.4)	8 (1.0)	2 (0.7)	68 (1.3)
Hematologic complications, *n* (%)	2 (1.1)	10 (2.3)	3 (0.7)	40 (1.4)	10 (1.2)	10 (3.3)	75 (1.5)
Thrombocytopenia, *n* (%)	0 (0)	0 (0)	0 (0)	4 (0.1)	1 (0.1)	1 (0.3)	6 (0.1)
Neutropenia, *n* (%)	2 (1.1)	10 (2.3)	3 (0.7)	36 (1.2)	9 (1.1)	9 (3.0)	69 (1.3)
Infectious (other), *n* (%)	6 (3.2)	13 (2.9)	19 (4.6)	73 (2.5)	21 (2.5)	2 (0.7)	134 (2.6)
Sepsis, *n* (%)	5 (2.6)	7 (1.6)	13 (3.2)	34 (1.2)	12 (1.5)	1 (0.3)	72 (1.4)
ARDS, *n* (%)	0 (0)	2 (0.5)	1 (0.2)	12 (0.4)	3 (0.4)	1 (0.3)	19 (0.4)
Hyponatremia, *n* (%)	1 (0.5)	4 (0.9)	5 (1.2)	27 (0.9)	6 (0.7)	0 (0)	43 (0.8)
Congenital varicella, *n* (%)	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.04)

other age groups, complications tend to be more severe, which may justify the need for a longer hospital stay.[7,20]

In our study, the number of admitted cases has varied unevenly. After the introduction of the vaccine in the market in 2003, the number of hospitalizations did not reveal a decreasing pattern, with the highest peak of hospitalizations being recorded in 2007. This is probably due low varicella vaccine coverage in children. In consonance with the World Health Organization recommendations, the Pediatric Infectious Diseases Society and Pediatric Portuguese Society recommend that this vaccine be given only to adolescents without previous varicella-zoster virus infection and children in close contact with immunodeficient patients, outside a National Vaccination Schedule that can assure a high vaccine coverage.[21]

Because varicella is not a mandatory notifiable disease in Portugal, we are unable to calculate the percentage of varicella infections that required hospitalization. Nonetheless, a Portuguese study revealed that, from a total of 215 728 people in the community managed during a whole year, 1270 developed varicella, with only 2 of them needing hospitalization: 1 aged <1 year and the other 1 an adult.[22]

Most hospitalizations occurred between April and August, with a peak in June and July. An Australian study that was focused on seasonal varicella variation had similar results to ours.[23] Similarly, data from Turkey and France presented a peak in spring and early summer months,[24,25] opposite to Sweden, United Kingdom, and Canada, with most cases occurring during winter to spring (school year) and falling during summer vacation.[26,27] Seasonal variation is yet to be explained, with suggested explanations for these variations being geographical differences in varicella epidemiology, differences in school calendar and in activities involving the gathering of susceptible populations.[23]

Complications were reported in ~37% of cases (Table 2), and, as expected, the most common were dermatologic, with necrotizing fasciitis occurring in 0.5% of cases. Severe neurologic complications occurred in 4.4% of cases, noteworthily encephalitis and more commonly in patients age >4 years. Respiratory complications, mainly pneumonia, were reported in 5.1% of children, and life-threatening complications, such as sepsis or acute respiratory distress syndrome, were reported in ∼2% of children. This is consistent with other studies, in which dermatologic, neurologic, and respiratory complications are the 3 most commonly associated with varicella, although the incidence of each varies between countries.[16–18,26,28,29] This can be explained by not totally understood differences between populations, such as climatic factors and population density.

We estimated that ICU admissions were ∼1%. A total of 8 deaths (0.2%) were registered during this period, consistent with the percentage found in other European countries.[16,26,28,30] This number reveals that despite being commonly a benign disease, varicella can lead to serious and fatal complications.

We did not assess complications in at-risk groups because there were only a few cases codified as immunosuppressed. Our cases could have been underestimated because we did not consider all ICD-9-CM codes corresponding to secondary immunodeficiency (eg, immunosuppression) because the list would be too extensive for the scope of this work.

The mean direct cost related to the hospitalizations was ∼1389€ (1680.69 USD). It would be interesting to make a more realistic approximation of costs in a future study, as it was done in Hungary.[19] It is important to bear in mind that the full financial burden related to varicella hospitalizations is grossly underestimated because we took into account only the values established by the Ministry of Health for reimbursement, according to the diagnosis-related group in question, and other costs related to the number of days parents missed from work, follow-up of patients, and burden of sequalae were not considered. Varicella vaccine has already been proven to be cost-effective, as revealed by a Canadian study focusing on the economic evaluation of varicella vaccination and finding that it is cost saving and highly cost-effective from the societal and health care perspective.[31] Also data from Italy, France, and Germany state that a routine varicella vaccination program appears to be cost saving, from both a societal and a third-party payer perspective.[32,33]

We found a statistically significant difference in the hospitalization costs between the patients with varicella as a primary or secondary diagnosis. This might be explained by the fact that when varicella is coded as a secondary diagnosis, the primary diagnosis may be a more severe sequelae of the disease, thus leading to more costs of care (eg, respiratory failure as a varicella complication). One particular example is in the case of transferred patients, in which the probability that the main diagnosis is not varicella is high and is justified when the patient needs resources that the first hospital does not have and that will condition the main diagnosis selection in the hospital receiving the patient.

There are some limitations in our study that must be considered, mainly because of the codification process. The hospital admission may have occurred for another reason, regardless of the simultaneous diagnosis of varicella, and a single code might have been attributed as a diagnosis to a patient, underestimating varicella cases or coding only varicella itself. In several studies with the same design as ours, researchers opted for using only varicella-related codes to identify complications (052.X).[15,34,35] To minimize the risks of underrepresenting complications, we decided to include the specific code corresponding to each of the main complications related to varicella infection.

There was also relevant information missing because of the retrospective nature of the study. Concerning complications, it was not possible to assess their severity, which would be important when interpreting our data, namely the LOS. Duration and indication for antibiotics were also not able to be assessed. Regarding the calculation of rates, for the first year of life, there is no breakdown of the population for each month of age in the available data and, as such, in the case of age groups <1 year, the population was estimated assuming a similar distribution over the months of age, which makes the rates calculated for these age groups an approximation.

As for reporting limitations, we were not able to estimate a real rate between hospitalizations and children infected with varicella, as done in other countries,[36,37] because varicella is not a mandatory notifiable disease in Portugal. We also could not assess the real number of vaccinated children and compare the pattern of hospitalizations between vaccinated and unvaccinated children, as has already been done in other countries.[38–42]

With this study, we believe we have provided important epidemiological information on varicella admissions in mainland Portuguese hospitals, which could be useful for considering universal varicella vaccination in the future.

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