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Considering recombinant herpes zoster vaccine for fragile pediatric patients: A new opportunity

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ABSTRACT

Background: A recombinant vaccine is approved to prevent herpes zoster (HZ) in adults ≥50 years and immunocompromised individuals ≥19 years. However, in children, the live attenuated vaccine remains the only prevention strategy against varicella zoster virus (VZV), with only one trial evaluating the safety and immunogenicity of GlaxoSmithKline's HZ subunit candidate vaccine in immunocompromised children.
Objectives: To estimate VZV burden in our third level pediatric hospital and identify high-risk pediatric groups for its occurrence and complications to explore the need for an inactivated vaccine.
Methods: We reviewed VZV/HZ hospital discharge codes and positive VZV molecular tests at Meyer Children's Hospital from January 2018 to May 2023. We categorized patients based on their vaccination status as unvaccinated, partially vaccinated (single dose), or fully vaccinated (complete two-dose regimen). 96 controls from the same Departments and period were also included to assess VZV vaccine effectiveness.
Results: Of 48 patients with VZV (52 % female; median age: 11.6 years [IQR: 7–14.2]), 10 had chickenpox and 38 HZ; 2/48 (4.2 %) received 2 doses of vaccination, 10/48 (20.8 %) were immunized with 1 dose and 36/48 (75 %) were unvaccinated. Immune-related comorbidities were present in 20/48 (42 %) patients, and among those with HZ requiring hospitalization, comorbidities strongly predicted admission (OR 4.71; 95 % CI, 1.23–20.39; $p = 0.028$). Full vaccination was more frequent in controls (43/96, 45 %) than in cases (2/48, 4.2 %; $p < 0.001$).
Conclusions: In our cohort, many cases had comorbidities contraindicating the live attenuated vaccine. If proven safe and effective, the recombinant HZ vaccine could offer a preventive option for immunocompromised children ineligible for live viral vaccines.

1. Introduction

The varicella-zoster virus (VZV), a member of the herpesvirus family, is the causative agent of varicella (chickenpox) and herpes zoster (shingles) [1,2]

Vaccination is a key preventive strategy against both chickenpox and shingles, however for the latter, a vaccine is only available for the adult population.

In immunocompetent children, varicella typically presents as a mild illness, marked by a distinctive, itchy, vesicular rash although serious

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complications can occur [3]. Newborns [4,5] and immunocompromised individuals are at higher risk of severe infection disseminated to lungs, liver, central nervous system (CNS) [6] and secondary bacterial infections, requiring hospitalization and sometimes resulting in death. After the primary infection, VZV enters a latent phase within sensory ganglia [7,8]. Advanced age and conditions that compromise the immune system increase the risk of developing herpes zoster (HZ) [9,10] characterized by a painful, vesicular rash with a dermatomeric distribution [3].

The postherpetic neuralgia (PHN) is the most common HZ's complication; further and feared clinical patterns include HZ ophthalmicus (HZO), Ramsay Hunt Syndrome, disseminated skin disease, visceral involvement, recurrent HZ, VZV-vasculopathy, and CNS involvement in form of myelitis, meningitis, and encephalitis [10–12].

Although they represent a relatively small proportion of overall HZ cases, immunocompromised populations significantly contribute to the public health burden due to their increased risk of complications and atypical presentations [13].

Children can benefit from the varicella vaccine, developed in 1970 using a live attenuated virus (Oka strain) and widely administered globally [14]. In Italy, it's mandatory for children born since 2017 (1st dose at 13–15 months and 2nd dose at 5–6 years of age) and in Tuscany it's offered optionally in combination with the vaccination against measles, mumps, and rubella (MPR) since 2008. The effectiveness of varicella vaccination is well-supported by data showing a significant reduction in disease incidence and hospitalizations [14–18], along with a good safety profile and rare cases of severe and disseminated Oka strain infection in children diagnosed with immunodeficiency only after vaccination [19].

For HZ, the first vaccine that became available is a live attenuated VZV vaccine approved for the prevention of HZ and PNH in individuals aged 50 years or older. Although the efficacy of the live zoster vaccine has been established, serious and fatal adverse events have been reported in patients with immune system dysfunctions for which vaccination remains not recommended [2,20]. Paradoxically, individuals with T-lymphocyte immunodeficiency and those undergoing certain immunosuppressant therapies who cannot receive these live attenuated vaccines [21] are also those most at risk for severe VZV and HZ complications, highlighting the need for herd immunity and alternative protection strategies.

In 2017 the Food and Drug Administration (FDA) approved the recombinant Zoster Vaccine, a subunit vaccine composed of recombinant glycoprotein E combined with the novel adjuvant AS01B [22] with higher effectiveness against HZ and PHN [23] compared to the live attenuated zoster vaccine. This vaccine, being non-replicating, is the first herpes zoster vaccine approved for use in immunocompromised populations [24], although the benefit for pediatric patients has not been explored. The Centers for Disease Control and Prevention (CDC) recommends two doses of recombinant-HZ vaccine (separated by 2 two to 6 six months) for the prevention of HZ and HZ-related complications in all adults aged 50 years and older and in adults aged ≥19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy (including patients with cancer, hematological malignancies requiring hematopoietic stem cell transplantation - HSCT, HIV or autoimmune and inflammatory conditions) [24].

In this context, the goal of our study is to determine the burden of pediatric VZV infection and to characterize thoroughly affected patients, with a particular focus on comorbidities and vaccination status. This approach will help us to identify the subset of pediatric patients who might benefit from the recombinant vaccine, once approved in this population.

2. Materials and methods

2.1. Study population

We conducted a retrospective observational study including patients aged 0 to 18 years who were treated at Meyer Children's Hospital (Florence, Italy) from January 2018 to May 2023 for varicella or HZ. A search was carried out using the terms "VZV", "varicella", "herpes" and "zoster" in the electronic records of the Laboratory, among the hospital discharge summaries and outpatient visits. This led to the identification of patients followed by the specialistic Units of Gastroenterology, Oncology-Hematology, Rheumatology, Immunology, Hepatology, Infectious Diseases or admitted to the Emergency Department. For each patient, a review of medical records was conducted to define the medical history, the vaccination status, and the need for hospitalization. Based on comorbidities, patients were divided as follows: i) children with diseases affecting the immune system (primary or secondary immunodeficiencies due to immunosuppressive therapies); ii) patients with other comorbidities and iii) healthy subjects. The vaccination status was verified on the collective prevention health information system (SISPC). Patients were then categorized on their vaccination status as unvaccinated, partially immunized with a single dose, or fully immunized with a complete two-dose regimen.

Finally, we conducted a test-negative control study to assess the effectiveness of the VZV vaccine preventing chickenpox and HZ. We selected 96 patients who, during the same period, presented to the Emergency Department or to the same specialistic Units of the cases, with clinical manifestations that could suggest VZV infection but tested negative for VZV through PCR. Also in this case, comorbidities were assessed through medical records, and varicella vaccination coverage was evaluated using the regional SISPC system.

2.2. Ethic statement

This study has been performed as part of the routine clinical activity and data collected are included in NETVAC registry, approved by Regional Pediatric Ethical Committee of Tuscany in September 2020 (CEP approval number 208/2020). All patients had given their consent to the use of their anonymized personal data for research purposes.

2.3. Definition of Herpes Zoster or Varicella infection

The diagnosis of HZ and varicella was defined based on:

1) clinical cutaneous manifestations and/or
2) positivity for VZV polymerase-chain reaction (qPCR, Argene, BioMerieux, France) on skin swab, blood, or cerebrospinal fluid and/or
3) seroconversion indicative of acute infection (positivity for VZV IgM; chemiluminescent immunoassay (CLIA) technology - LIAISON XL System, DiaSorin, Saluggia (VC), Italy, with seropositive samples defined as those with antibody titers >150 mIU/mL)

2.4. Endpoint

The main goal of our study was to define the burden of varicella and HZ in the experience of our Pediatric Hospital, evaluating the factors associated with an increased risk of hospitalization and complications and the previous immunization to define pediatric patients who could benefit from vaccination with recombinant HZ vaccine.

2.5. Statistical analysis

The demographic and clinical data were summarized using standard descriptive statistics. The distribution of data was assessed by visually analyzing the boxplot for each variable. Continuous variables were presented as mean ± standard deviation (SD) in case of normal

distribution or as median [inter-quartile range (IQR)] in case of skewed distribution and compared between groups using an unpaired-samples *t*-test or a nonparametric Wilcoxon-Mann-Whitney test, respectively. Kruskal-Wallis method was used to test all continuous covariates across more than two groups. Categorical variables were expressed as absolute and relative frequencies, and group comparisons were performed using the $\chi 2$ test or Fisher's exact test when the sample size is less than 10 in any of the cells within the contingency table.

To identify the predictors of hospitalization, we used a logistic regression model, and the results were expressed as odds ratios (ORs) with the corresponding 95 % confidence intervals (CIs).

All tests were two tailed, and values of $p < 0.05$ were considered significant. Statistical analyses were performed using R version 4.2.1 (R foundation, Vienna, Austria) and graphical representations were created with GraphPad Prism software version 9.0.

3. Results

Descriptive analysis of case - population: demographics, diagnosis, and clinical presentation.

A total of 48 patients were included, of whom 38 (79.2 %) had a diagnosis of HZ and 10 (20.8 %) a diagnosis of varicella. The main characteristics of the enrolled population are summarized in Table 1. The diagnosis had molecular confirmation through PCR in 27/48 patients (56.2 %), of these 2 from blood, one from cerebral spinal fluid and the others from skin swabs. Diagnosis was based on clinical assessment, without VZV testing, in 20/48 (41.7 %) patients and in one case through antibody response indicative of acute infection (positivity for VZV IgM). As expected, varicella patients were significantly younger compared to patients with HZ [6.5 (1.2; 7.1) vs. 12.7 (9.5; 14.8) years, $p = 0.001$]. The majority of HZ cases occurred in children aged 9 to 16 years; for varicella, the peak age was 2 years.

Table 1
Demographic and clinical characteristics of the enrolled population and categorized by Herpes Zoster and Varicella diseases.

Variables	Overall	Herpes Zoster Population	Varicella Population	*P* values
No. of patients (%)	*48*	*38 (79.2)*	*10 (20.8)*	
Female sex - no. (%)	*25 (52.1)*	*18 (47.4)*	*7 (70)*	*0.358*
Age - years	*11.6 [7; 14.2]*	*12.7 [9.5; 14.8]*	*6.5 [1.2; 7.1]*	***<0.001***
Clinical Presentation – no. (%)				*1*
Cutaneous forms	*46 (95.8)*	*36 (94.7)*	*10 (100)*	
Encephalopathy/ Myopericarditis	*2 (4.2)*	*2 (5.3)*	*0 (0)*	
Diagnosis – no. (%)				*0.631*
Clinical	*20 (41.7)*	*17 (44.7)*	*3 (30)*	
Positive PCR	*27 (56.2)*	*21 (55.3)*	*6 (60)*	
Serology	*1 (2.1)*	*0 (0)*	*1 (10)*	
Immunity Status – no. (%)				0.639
Immunized with 2 doses	*2 (4.2)*	*2 (5.2)*	*0 (0)*	
Immunized with 1 dose	*10 (20.8)*	*9 (23.7)*	*1 (10)*	
Unvaccinated	*36 (75)*	*27 (71)*	*9 (90)*	
Comorbidities – no. (%)				*0.120*
Immunological diseases	*20 (41.7)*	*17 (44.7)*	*3 (30)*	
Non-immunological disease	*3 (6.2)*	*1 (2.7)*	*2 (20)*	

Baseline characteristics of the overall population ($n = 48$) and divided by Herpes Zoster ($n = 38$) and Varicella ($n = 10$) diseases. Data are expressed as number (%) and median (25th; 75th percentile). Significant values are reported in bold. "PCR" = Polymerase Chain Reaction. Statistics: Wilcoxon-Mann-Whitney, Fisher's exact and Chi-square ($\chi 2$) tests.

Regarding clinical manifestations, 46/48 (95.8 %) patients showed exclusively cutaneous forms of the disease. Two serious clinical complications were observed in the HZ group: a 16-year-old female with a confirmed natural history of infection developed encephalitis, and a 17-year-old unvaccinated male suffered myopericarditis. Remarkably, none of these patients had any other comorbidities. Regardless of underlying diseases, all patients received antiviral therapy.

3.1. Comorbidities

Approximately half (48 %) of all the patients included had comorbidities (Fig. 1A and B), of which 20 (41.7 %) had immune system disorders, with no significant differences between patients with VZV and those with HZ ($p = 0.120$, Table 1). The type and the frequency of the underlying diseases are described in Table 2. There was no significant difference in median age at onset of HZ between patients with and without comorbidities [12.7 (10.4; 14.7) and 13 (8.5; 14.4) years, respectively; $p = 0.759$].

3.2. Previous immunization

Among patients with VZV/HZ infection, only 2/48 (4.2 %) received two doses of the varicella vaccine, while 10/48 (20.8 %) received only one dose (Fig. 2A); through these 3/10 (30 %) had secondary immunosuppression contraindicating the completion of the vaccination cycle. The remaining 36/48 (75 %) patients did not receive any dose. Among these, 15/36 (41.7 %) were born after 2008: 6 out of 15 (40 %) had immunological comorbidities for which the currently available vaccination was not recommended; 5/15 (33.3 %) were unvaccinated due to parental choice, and the remaining 4/15 (26.7 %) were under 15 months old at the onset of VZV infection.

The immune status of the entire case-cohort is represented in Table 1 *and* Table 3. Analyzing separately patients with varicella and shingles, we found that among children with chickenpox 9/10 were naïve and 1/10 (10 %) received only 1 dose of vaccination. Within HZ patients 2/38 (5.2 %) were immunized with a complete vaccination cycle and 9/38 (23.7 %) received only one dose of vaccination.

3.3. Hospitalization

Among the 48 case-patients who came to our attention, 26 (54.2 %) were hospitalized, with a median [4;11] length of stay of 7.5 days. Of note, 50 % of these patients had comorbidities. Specifically, all children with chickenpox required hospitalization, of which one patient died after a month of hospitalization from acute respiratory failure due to progression of the underlying disease (acute lymphocytic leukemia).

In the HZ population, 16/48 (42.1 %) patients required inpatient treatment, while the others received outpatient care. Univariable logistic regression analysis (Table 4) revealed that age, gender, and naïve immune status had no effect on the likelihood of hospitalization. Importantly, the presence of comorbidities was the unique strong predictor of hospitalization, with an average 5-fold higher probability of hospitalization compared to otherwise healthy patients (Odds Ratio, 4.71; 95 % CI, 1.23–20.39; $p = 0.028$, Table 4).

Consistently, patients who were hospitalized had significantly more comorbidities than those who required only outpatient treatment ($p = 0.047$, Fig. 1B). Conversely, when examining immunity status, there was no distinction between hospitalized and non-hospitalized HZ individuals ($p = 0.743$).

3.4. Case-control study

After analyzing the cohort of VZV patients, we considered the control

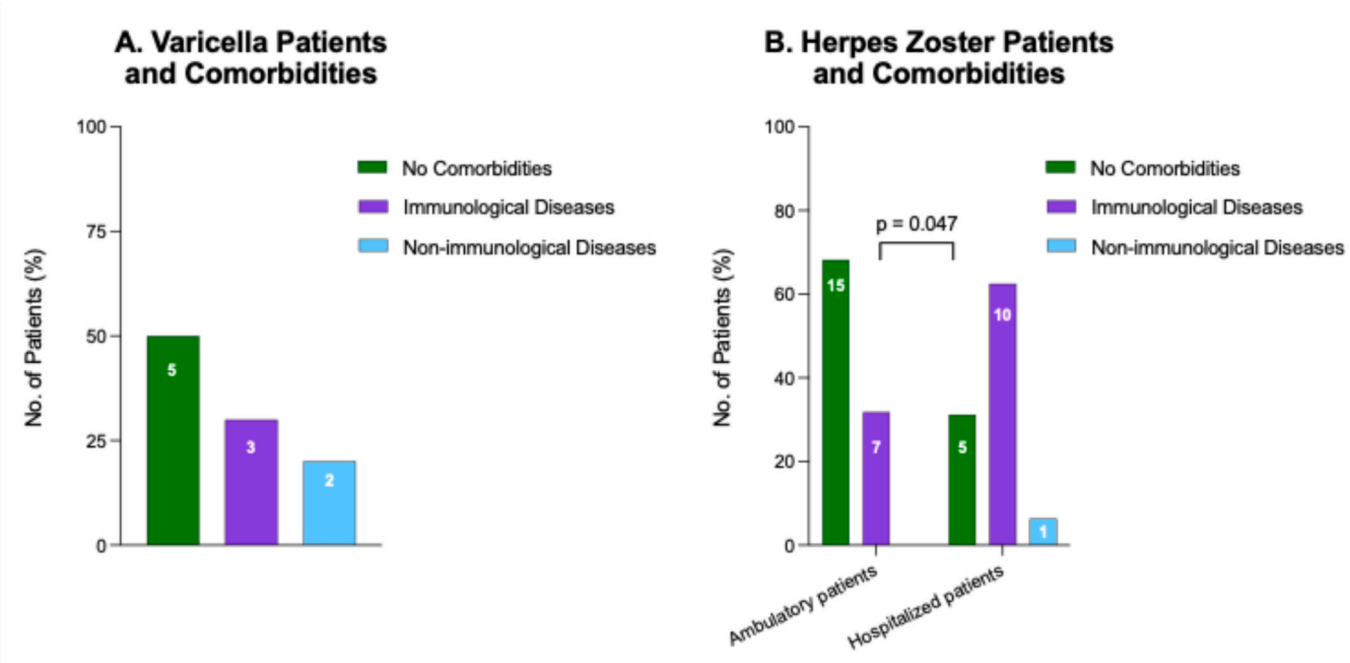

Fig. 1. Immunization Status and Comorbidities. The figure illustrates the number of patients with chickenpox (A) and shingles (B) in relation to comorbidities. For HZ patients, it further differentiates between inpatients and outpatients. Statistical analysis: Fisher's exact test.

Table 2
Underlying diseases and their frequency in both HZ and varicella groups.

Disease	No. patients
Herpes Zoster inpatients	
o Juvenile idiopathic arthritis (JIA)	1
o Chronic liver disease	1
o Epilepsy, obesity	1
o Brain tumor	2
o Blackfan-Diamond syndrome undergoing stem cell transplantation	1
o Systemic lupus erythematosus (SLE)	1
o Acute myeloid leukemia (AML)	2
o Hodgkin's lymphoma	1
o Dermatomyositis	1
Herpes Zoster outpatients	
o Acute lymphocytic leukemia (ALL)	2
o Down syndrome, ipotyroidism	1
o Behcet's disease, Hashimoto thyroiditis	1
o Celiac disease	1
o Inflammatory bowel disease (IBD)	1
o CD8+ lymphopenia	1
Varicella	
o Chronic liver disease	2
o Epilepsy	2
o Acute lymphocytic leukemia (ALL)	1

group of 96 patients. Importantly, evaluating age, sex, hospitalization, and comorbidities, no significant differences were found between cases and control-patients (Table 5). Notably, 43/96 control patients (44.9 %) had completed the full vaccine cycle, a significantly higher proportion than in the case cohort (2 out of 48, 4.2 %; $p < 0.001$, Fig. 2B). As a sensitivity analysis, these findings were further corroborated by examining only the subset of 27 cases with a positive PCR result, among which only 1 (3.7 %) had been vaccinated—a proportion that remains significantly lower than that of the vaccinated controls ($p < 0.001$).

Crucially, when examining the relationship between vaccination status and comorbidities among the control group, 30 out of 56 patients without comorbidities (53.6 %) were vaccinated, a significantly higher proportion compared to 11 out of 36 (30.5 %) with comorbidities impairing immune system ($p = 0.030$).

4. Discussion and conclusion

The primary care setting plays a crucial role in the management of chickenpox and HZ and laboratory tests or specialist consultations are generally not required [25]; however, for atypical cases or those involving immunocompromised children, diagnostic confirmation tests and a more cautious approach become indispensable. This retrospective study shows that shingles has not a negligible weight in the pediatric age when there are currently no prevention approaches. Of our cohort of cases 6/15 (40 %) patients, who were born after 2008, could not receive any dose of live vaccine cause immune impairment, and 3/10 (30 %) did not complete the vaccination schedule for the onset of diseases involving immune system (one of these patient likely lost VZV protection after HSCT). Among patients with chickenpox, nobody was fully vaccinated and 30 % of these children were affected by diseases for whom live attenuated vaccine currently approved in pediatrics was contraindicated. In our cohort, immune-related comorbidities in patients with HZ were associated with a higher risk of hospitalization but did not correlate with a more severe course of the infection. However, the only death was reported in a patient with leukemia: while varicella was likely not the primary cause, it is noteworthy that she had a high viremia (qPCR, cycle threshold 27). Other fatal cases are reported in patients with VZV infection and lymphoproliferative diseases due to fulminant liver failure [26] and visceral dissemination of the virus even without skin involvement [27,28], and in children with LLA the risks associated with the current varicella vaccination may outweigh the benefits, stressing the importance of herd immunity [29] and new vaccination strategies.

One of the main objections to the spread of universal VZV vaccination is that the reduced circulation of the wild-type virus would have led to a reduction in exogenous boosters and a weakening of the defenses against the reactivation of VZV [30]. However, cell-mediated immunity can be boosted by subclinical reactivation of VZV determining endogenous boosters that maintain efficient immune defenses to prevent HZ [31–33] and previous studies showed that HZ has a lower incidence in vaccinated individuals [34,35], in whom, in most cases, it is caused by the wild-type strain [36,37].

In our study, through case-control analysis, the broader vaccination

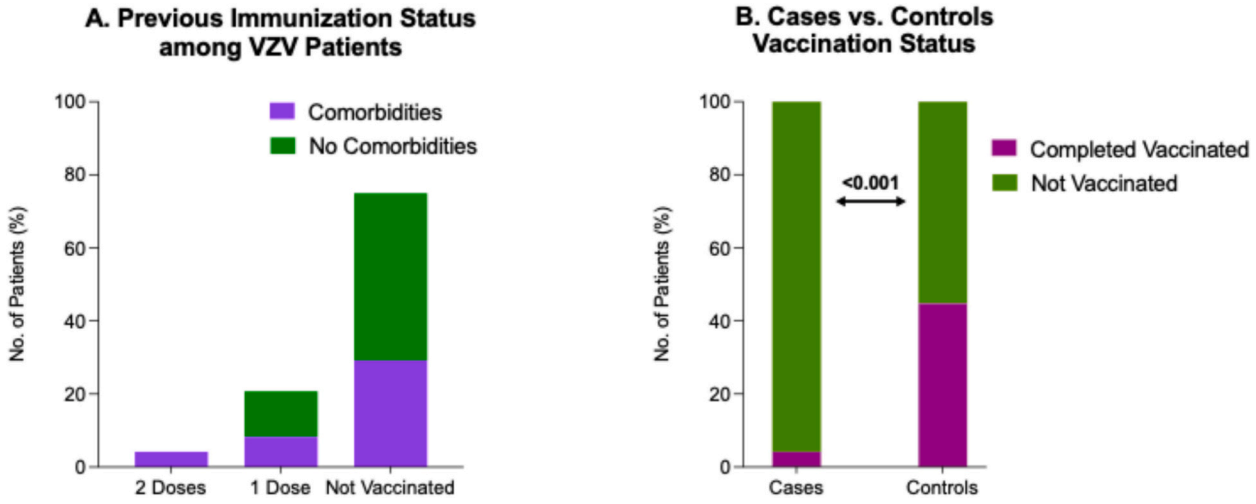

Fig. 2. Overview of Vaccination Status in Cases and Controls. Bar plots display the percentage of vaccination status among patients with VZV infection, stratified by comorbidities (A), and comparing cases to controls (B).

Table 3
Demographic and clinical characteristics at baseline based on the immunity status.

Variables	Immunized with 2 doses	Immunized with 1 dose	Unvaccinated	P values
No. of patients (%)	*2 (4.2)*	*10 (20.8)*	*36 (75)*	
Herpes Zoster – no. (%)	*2 (100)*	*9 (90)*	*27 (75)*	–
Varicella – no. (%)	*0 (0)*	*1 (10)*	*9 (25)*	–
Female sex - no. (%)	*2 (100)*	*6 (60)*	*17 (47.2)*	*0.438*
Age – years	*12.1 [10.6–13.6]*	*7.1 [5.9–13.7]*	*11.7 [8.6–14.4]*	*0.585*
Clinical Presentation – no. (%)				
Cutaneous forms	*2 (100)*	*10 (100)*	*34 (94.4)*	*0.567*
Encephalopathy/ Myocarditis/ Pericarditis	*0 (0)*	*0 (0)*	*2 (5.6)*	
Comorbidities – no. (%)				*0.538*
Immunological diseases	*2 (100)*	*4 (40)*	*14 (38.9)*	
Non-immunological disease	*0 (0)*	*0 (0)*	*3 (8.3)*	

Data are presented as number (%), mean (CI) or median (25th; 75th percentile) (range). Statistics: Kruskal-Wallis chi-squared test, Fisher's exact and Chi-square ($\chi 2$) tests.

Table 4
Predictors of Hospitalization in Herpes Zoster Population.

Herpes Zoster Population		
Variables	Odds Ratio (95 % Cis)	P values
Age (years)	1.12 (0.9–1.3)	0.198
Gender - Female	Reference	–
Male	0.8 (0.2–3.1)	0.782
Immunity Status – Unvaccinated	Reference	–
Immunized with 1 dose	0.3 (0.1–1.2)	0.092
Immunized with 2 doses	0.6 (0.02–16.9)	0.756
Comorbidities – None	Reference	–
Yes	4.7 (1.2–20.4)	**0.028**

Predictors of Hospitalization based on logistic regression analysis. In bold are reported significant values. Statistic: univariable logistic regression model.

Table 5
Demographic and Clinical Characteristics in $N = 96$ controls compared to N = 48 case patients included in the study.

Variables	Cases	Controls	P values
No. of patients (%)	48	96	
Females - no. (%)	25 (52.1)	39 (40.6)	0.260
Age – years	11.6 [7.0;14.2]	9.1 [6.5; 13.3]	0.237
Comorbidities – no. (%)			0.690
Immunological diseases	20 (41.7)	36 (37.5)	
Non-immunological diseases	3 (6.3)	4 (4.2)	
Hospitalization, no. (%)	26 (54.2)	54 (56.3)	0.953
Immunity status- Vaccinated, no. (%)	2 (4.2)	43 (44.8)	**<0.001**

Demographic and clinical characteristics of the control population compared to case patients. Data are expressed as number (%) and median (25th; 75th percentile). Significant values are reported in bold. Statistics: Wilcoxon-Mann-Whitney, Fisher's exact and Chi-square ($\chi 2$) test.

coverage among VZV-negative patients, especially those without comorbidities, highlighted the strong effectiveness of the currently available vaccine in preventing varicella and HZ in the pediatric population.

The increase in the incidence of HZ, preceding the widespread use of the varicella vaccine, is likely multifactorial and related to factors such as the aging population and the growing number of immunocompromised individuals [38] who are ineligible for live attenuated vaccines underscoring the need to explore alternative preventive measures including a combined vaccination program for varicella and shingles to limit the increased incidence of HZ [30,39].

Focusing on vaccination strategies, the recombinant HZ vaccine, due to its high immunogenicity, is currently approved for immunocompromised adults aged ≥19 years but not yet in the pediatric age.

However, given the increasing number of pediatric patients undergoing immunosuppressive therapies due to malignant oncological diseases, solid organ transplants and autoimmune diseases, this recombinant vaccine could also play a role in immunocompromised children. Leung et al. [40]showed that VZV infections represent a major cause of morbidity in children after HSCT, especially in the first-year post-transplant, when they are not yet immunocompetent enough to safely receive the live attenuated varicella vaccine. Berman JL et al. evaluated a cohort of 310 pediatric patients who underwent HSCT: of

76/310 who developed HZ, PHN occurred in 29 %, disseminated skin involvement in 20 % and visceral organ dissemination (liver, eye, lung and CNS) in 7 % [41]. A recent review by L.S. Abbuehl et al. highlighted the high mortality rates associated with VZV-related encephalitis and meningitis, varying across different studies. Notably, two studies reported mortality rates of 33 % in a cohort of patients requiring intensive care [42], and 36 % in a cohort where all fatal infections were complicated by stroke and/or myelitis [43].

The efficacy, immunogenicity and safety of the recombinant zoster vaccine has been studied in several immunocompromised adult populations [44–49]; in the pediatric age a phase II randomized multicenter study (*clinicaltrials.gov*, NCT04006808), is currently ongoing to evaluate the reactogenicity, safety, and immunogenicity of GlaxoSmithKline's pediatric Herpes Zoster subunit candidate vaccine (PED-HZ/su) on a 2-doses schedule for immunocompromised subjects aged 1–17 years who have undergone renal transplantation.

A potential role for the recombinant vaccine could also be of interest for the immunization of patients not eligible for the live attenuated VZV vaccine, as suggested in the study by Badolato et al. focused on an alternative approach to VZV prevention in a child with mild/moderate T-CD4 lymphopenia [50].

Our data, based on the experience of a tertiary-level institution and the analysis of a small sample-size, reflect only a fraction of the pediatric population, and may not perfectly mirror the epidemiology of HZ and varicella in children. Moreover, a possible objection to the case-control study is that in 20 out of 48 patients with VZV infection, the diagnosis was made without laboratory confirmation. However, the diagnosis of varicella or HZ is primarily clinical, and etiological investigations are useful in doubtful, atypical cases or in vulnerable patients. Nevertheless, in our cohort, the higher prevalence of vaccinated individuals among the controls is maintained even when considering only case-patients with molecular confirmation.

In conclusion, our study highlighted that HZ does not only affect the elderly population or people with comorbidities, who are at higher risk of hospitalization, but also otherwise healthy children with two serious complications occurred in patients without underlying conditions and both unvaccinated.

Further research and large studies are essential to define the impact of HZ infection in children and identify patient categories that could benefit from new preventive strategies, including the HZ subunit vaccine.

CRediT authorship contribution statement

A. Mollo: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **M. Peri:** Writing – review & editing, Visualization, Validation. **L. Lodi:** Writing – review & editing, Visualization, Validation. **A. Gissi:** Writing – review & editing, Visualization, Validation. **P. Lionetti:** Writing – review & editing, Visualization, Validation. **E. Marrani:** Writing – review & editing, Visualization, Validation. **M.V. Mastrolia:** Writing – review & editing, Visualization, Validation. **A. Tondo:** Writing – review & editing, Visualization, Validation. **V. Tintori:** Writing – review & editing, Visualization, Validation. **I. Sardi:** Writing – review & editing, Visualization, Validation. **G. Indolfi:** Writing – review & editing, Visualization, Validation. **S. Trapani:** Writing – review & editing, Visualization, Validation. **L. Galli:** Writing – review & editing, Visualization, Validation. **E. Venturini:** Writing – review & editing, Visualization, Validation. **V. Astorino:** Writing – review & editing, Visualization, Validation. **C. Azzari:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **S. Ricci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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