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Effect of the varicella vaccination implementation on the development of herpes zoster in children and adolescents

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Abstract

Herpes zoster (HZ) is an infectious disease caused by latent varicella-zoster virus reactivation. There are conflicting reports on the varicella vaccine's effect on the incidence of HZ in children and adolescents. This study aimed to determine the impact of the single dose of varicella vaccination on HZ prevalence during childhood and adolescence. The study included children and adolescents aged <18 years who presented to the dermatology outpatient clinic between 2005 and 2019 and were diagnosed with HZ. Considering that the universal vaccination program started to be implemented in Turkey in 2013, non-vaccinated cases in the prevaccination period, vaccinated cases in the postvaccination period, and non-vaccinated patients in the postvaccination period were compared in terms of HZ prevalence and demographic features. After the initiation of the varicella vaccination program, the prevalence of HZ was found to decrease by 24.7% in all. The HZ prevalence was significantly reduced in vaccinated children, while the rate of decrease in non-vaccinated children was low (58.6% and 16.4%, respectively). The median age of the non-vaccinated cases in the postvaccination period (10 [min 0.5-max 17] years) was significantly higher compared to the other groups ($p < 0.001$). The number of cases aged <2 years was the highest in the vaccinated group ($p < 0.001$). Administration of a single dose of varicella vaccine was insufficient to decrease the prevalence of HZ <18 years of age. In the post-vaccination period, the frequency of HZ in unvaccinated cases increased in adolescence. In vaccinated children, HZ seems to develop at an earlier age.

KEYWORDS
herpes zoster (shingles,VZV), pediatric dermatology, vaccine, varicella

1 | INTRODUCTION

Herpes zoster (HZ) is an infectious disease characterized by painful vesicular lesions that emerge from the latent varicella-zoster virus's (VZV) reactivation. HZ usually develops in adulthood, and it is infrequent in childhood and adolescence. Although the incidence of HZ under 20 years differs from one population to another and the methodology used, it has been reported as 160 to 220 per 100,000 person-years.[1,2] While HZ is observed more frequently in children with malignancies, immunosuppression, HIV infection, or exposure to VZV before the age of 1 year, it does also occur in otherwise healthy children, albeit rarely.[3-7] Clinical manifestations in children are generally milder than those in adults, and postherpetic neuralgia is less seen in the former.[1]

The study was conducted in University of Health Sciences, Istanbul Training and Research Hospital, Istanbul, Turkey.

The first vaccine developed to prevent the disease is the "OKA strain," attenuated from the vesicular fluid in Japan in 1974. The application of single-dose varicella vaccine to healthy children started to be applied routinely in the United States in 1995. A reinforcement dose was added to the program in the United States in 2007 due to the increase in varicella infections at the ages of 4–6.[8] In 2013, the universal varicella vaccination program was initiated as a single dose at the 12th month in healthy children in Turkey. The coverage rate of varicella vaccine is >95% in Turkey.[9]

Along with the universal varicella vaccination program, a significant reduction in varicella infection has been achieved. Still, conflicting reports have begun to be published regarding the increase in the HZ incidence among children and adults. In some incidence studies and those based on mathematical models, it has been suggested that a single dose of the varicella vaccine is not sufficient to decrease the incidence of HZ. Therefore discussions about the need to administer a booster dose of the vaccine in children or the vaccination of adults for herpes zoster prevention have begun.[10-13] In contrast, other studies reported that universal vaccination programs had decreased the HZ incidence.[10,11,13-15]

Recently, we noticed an increase in the number of childhood patients with HZ. This study aimed to determine the impact of the universal varicella vaccination program on the prevalence of HZ in childhood and adolescents, and evaluate the demographic characteristics of these patients.

2 | MATERIAL AND METHODS

This study was approved by the local ethics committee of Istanbul Education Research Hospital (2011-KAEK-50, Date: October 25, 2019, No: 2034). Children and adolescents aged <18 years, who presented to the dermatology clinic of the hospital between 2005 and 2019 and received a diagnosis of HZ, were included in the study. Potential HZ cases were identified electronically using the ICD-10 code of B02.XX from the dermatology outpatient clinic files.

In order to reveal the effect of the universal varicella vaccination program on the pediatric and adolescent prevalence of HZ, 2013 was taken as the basis as the year in which this program was initiated in Turkey. Accordingly, the period from 2005 to 2012 was defined as the prevaccination period and 2013–2019 as the postvaccination period. Non-vaccinated patients who developed HZ in the prevaccination period were evaluated as Group 1, and those who developed HZ in the postvaccination period as Group 2.

Since a single dose of varicella vaccine was started to be administered to 12 month old children as of 2013 (born after January 2012) and no catch-up was applied, some of the HZ cases (born before January 2012) were non-vaccinated in the postvaccination period. Therefore, the cases in Group 2 were further divided into two subgroups as Group 2A and Group 2B, referring to the non-vaccinated and vaccinated HZ patients, respectively. The demographic characteristics of all cases were recorded.

In order to evaluate how the vaccination program affected the development of HZ in early childhood and adolescence, age categories were determined as under 2 years, 2–5 years, 6–10 years, and above 10 years, and comparisons were performed between the study groups according to these age categories.

2.1 | Statistical analysis

In the calculation of the HZ prevalence, the number of children and adolescents aged <18 years who presented to the dermatology clinic of Istanbul Education Research Hospital for any reason was taken as a denominator. The HZ prevalence was calculated by taking the ratio of the number of HZ cases aged <18 years over the total number of patients aged <18 years presenting during the same period. The prevalence values for Group 1, Group 2A, and Group 2B were separately calculated to demonstrate the impact of the vaccination program on the HZ prevalence among the vaccinated and non-vaccinated children. While estimating the HZ prevalence in the prevaccination period, the total number of children that presented to the dermatology outpatient clinic between 2005 and 2012 was taken as a denominator, for the postvaccination period (2013–2019), this value was calculated based on the denominators of the number of non-vaccinated and vaccinated children for Group 2A and Group 2B, respectively. The prevalence values of all three groups were compared.

Data were analyzed on Statistical Package for the Social Sciences (SPSS, version 22.0, Chicago, IL, USA) software. Numbers and percentages were used as descriptive statistics for categorical variables, and median, minimum and maximum values were obtained for numerical variables since the variables did not show normal distribution. In the analysis of numerical variables, the Mann-Whitney *U* test was used to compare two groups, and the Kruskal-Wallis test was employed to compare more than two groups. The Bonferroni correction was used to interpret the findings. The inter-group differences between categorical variables were analyzed using the chi-square and Fisher's exact tests. For all statistical tests, $p < 0.05$ was considered statistically significant.

3 | RESULTS

The number of pediatric patients diagnosed with HZ between 2005 and 2019 was 190. Eighty-eight (46.3%) patients were male, and 102 were female (53.7%). The mean age of the patients was 7.55 ± 4.18 years, with the median value being calculated as 7 (min:0.5, max:17) years. Seventy-one of the patients with HZ were in the prevaccination period, and 119 were in the postvaccination period. Table 1 presents the age distribution and gender characteristics of the cases in each group. When the median ages of the patients were compared, there was a statistically significant difference between Group 2A and the other two groups, with the patients' Group 2A being older

TABLE 1 Demographic characteristics of children with HZ in the prevaccination and postvaccination eras and their distribution by age categories

Cases of HZ, n (%)			
Characteristic	**Prevaccination era (Group 1)**	**Postvaccination era non-vaccinated (Group 2A)**	**Postvaccination era vaccinated (Group 2B)**
Gender			
Male	38 (53.5%)	43 (40.6%)	7 (53.8%)
Female	33 (46.5%)	63 (59.4%)	6 (46.2%)
Age at HZ diagnosis, years			
Median (min, max)	4 (0.9, 9)	10 (0.5, 17)	2 (1, 6)
Age categories			
< 2 years	5 (7%)[a]	1 (0.9%)[a,b]	3 (23.1%)[b]
2–5 years	33 (46.5%)[a]	5 (4.7%)[a,b]	7 (53.8%)[b]
> 10 years	33 (46.5%)	40 (37.7%)	3 (23.1%)
>10 years	0 (0%)[a]	60 (56.6%)[a]	0 (0%)
Total	71 (100%)	106 (100%)	13 (100%)

Note: Same superscripts (a, b) indicate group mean differences ($p < 0.05$).
Abbreviation: HZ, Herpes zoster.

($p < 0.001$) (Table 1 and Figure 1). There was no statistically significant difference between the three groups in terms of gender ($p = 0.203$).

HZ's prevalence in the <18-year-old sample was 384/100,000 for the prevaccination period and 289/100,000 for the postvaccination period. Following the universal vaccination program, there was a total decrease of 24.7% in the HZ prevalence (Table 2). When HZ cases in the prevaccination period and the vaccinated children in the postvaccination period were compared, there was a 58.6% decrease in the HZ prevalence among the vaccinated cases. The rate of patients younger than 2 years of age was higher among the vaccinated children (23% and 7%, respectively), but this difference was not statistically significant ($p = 0.103$) (Tables 1 and 2) (Figure 2). When the HZ cases in the prevaccination period and the non-vaccinated children in the postvaccination period were compared, there was a 16.4% decrease in the HZ prevalence among the non-vaccinated children in the postvaccination period. While the number of HZ cases aged <2 years was higher in the prevaccination era, a shift toward the adolescent period was observed among the non-vaccinated patients ($p < 0.05$). While there was no pediatric HZ case above 10 years of age before the vaccination program, more than half of the non-vaccinated patients in the postvaccination era were over 10 years old (56.6%) ($p < 0.001$) (Tables 1 and 2) (Figure 2).

The comparison of the vaccinated and non-vaccinated children in the postvaccination era revealed that the number of cases aged <2 years and < 5 years was higher in the vaccinated group ($P < 0.001$). Among the vaccinated children, the meantime from vaccination to HZ development was 1.8 years. Since only the children born after 2012 January were included in the vaccination program, the patients' maximum age in the vaccinated group for the study period was 7 years. Therefore, there were no cases older than 10 years in the vaccinated patient group, and thus the vaccinated and non-vaccinated cases could not be compared among the adolescents (Table 1) (Figure 2).

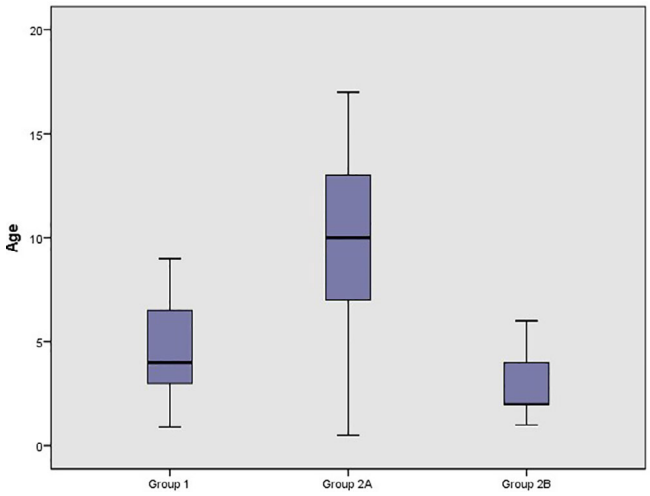

FIGURE 1 Median, minimum and maximum ages of the Herpes zoster cases in Group 1, Group 2A, and Group 2B

There was no statistically significant difference in pediatric HZ cases' seasonal distribution before and after 2013 ($p = 0.131$).

4 | DISCUSSION

Since 2002, universal varicella vaccination programs have been reported to decrease the number of varicella infections; however, there has been an increase in the HZ incidence, with the vaccine strain being suggested to have a lower protective effect against HZ.[13,16,17] Brisson et al. argued that mass vaccination would cause an epidemic HZ increase and that 50% of HZ cases were between 10 and 44 years of age.[18] The increase in HZ incidence with the implementation of vaccination programs is attributed to a reduction in

TABLE 2 Prevalence of HZ in children aged <18 years before and after the initiation of the universal varicella vaccination program

	Cases of HZ (n)	Number of children aged <18 years	Prevalence of HZ
Prevaccination era Group 1	71	18.476[a]	384/100,000
Postvaccination Era Group 2	119	41.221[b]	289/100,000
Group 2A (non-vaccinated)	106	33.026	321/100,000
Group 2B (vaccinated)	13	8.195	159/100,000

Abbreviation: HZ, Herpes zoster.
[a]Total number of children aged <18 years presenting to the hospital between 2005 and 2012.
[b]Total number of children aged <18 years presenting to the hospital between 2013 and 2019.

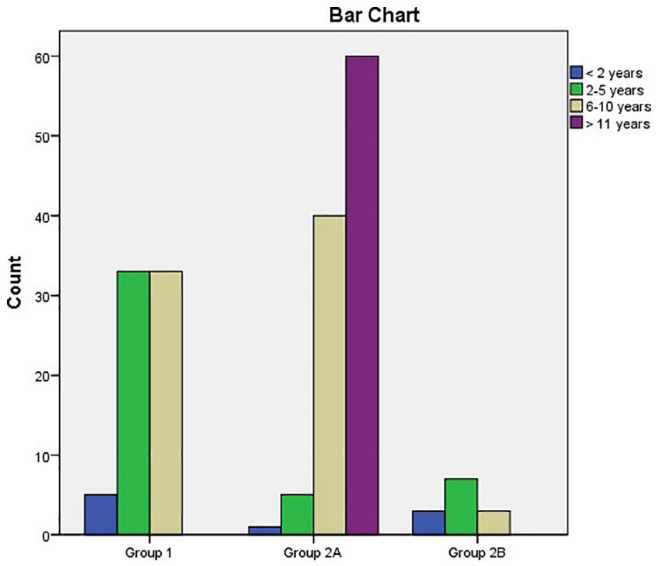

FIGURE 2 Distribution of the Herpes zoster cases in Group 1, Group 2A, and Group 2 B according to age categories

exogenous boosting effect. This hypothesis, defined by Hope-Simpson, suggests that exogenous exposure to people with VZV might boost specific immunity, and therefore decrease the risk of zoster in latently infected individuals.[19] In modeling studies based on the reduced exogen boosting effect, it is assumed that there will be a temporary increase in the HZ incidence over a period of 40–50 years after the start of vaccination programs, but at the end of this period, there will be a decrease again.[20-23] In light of these studies, it has been discussed whether booster varicella vaccination should be applied at the 18th month, 4–5 years, or the adolescent period or adults should be vaccinated against HZ. There has even been a mention of screening the requirement of varicella vaccination in developing countries and maintaining the aim of herd immunity.[10-12,24]

Recent long-term studies have shown that the HZ incidence was reduced in children and adolescents. In 2011, Weinman et al. found the HZ incidence in vaccinated children to be 79% lower than non-vaccinated children in a sample of under 20 years.[10] Kawai et al. detected a decrease in the HZ incidence in children under 10 years of age in contrast to the 4-fold increase in adults of advanced ages. Civen et al. reported that the HZ incidence was reduced by 55% in children aged under ten with the common implementation of varicella vaccination. Still, the incidence of HZ among adolescents was 63%.[11,25] It has been suggested that the decrease in HZ among vaccinated individuals may be due to the lower transmission of the vaccine virus to sensory nerves and less frequent reactivity.[26]

In Turkey, since a single dose of varicella vaccine was started to be administered to 12-month-old children as of 2013 (born after January 2012) and no catch-up was applied, children born before January 2012 were non-vaccinated in the postvaccination period. Thus we were also able to compare the vaccination program's effect on the development of HZ in vaccinated and non-vaccinated children. In our study, after the initiation of the varicella vaccination program, the prevalence of HZ was found to decrease by 24.7% in all. This rate of decline was lower compared to similar studies in the literature. When we separately evaluated the rate of decrease in prevalence in vaccinated and non-vaccinated children, we determined them as 58.6% and 16.4%, respectively. The results indicate that due to the single dose of vaccination and the absence of a catch-up vaccine application, there has not been a sufficient decrease in the wild-type strains in the environment. The reduction in the prevalence of HZ has remained at lower levels than expected especially in non-vaccinated cases.

In vaccinated children, HZ may occur with the activation of wild-type or vaccine strain of VZV.[10,27,28] Weinmann et al. detected the Oka strain in the vesicular fluid in half of the vaccinated cases that developed HZ and found the mean age of these cases to be lower (mean 2 years) than those with wild-type strains. The authors reported that the HZ incidence generally decreased with the vaccination program. Still, among the vaccinated children, the incidence of this disease was observed to increase in the 1–2 years age group.[10] Similarly, in our study, the HZ prevalence decreased by 58.6% in the vaccinated cases, but the mean age in these children decreased to 2 years. Similar to the literature, we determined the meantime from vaccination and HZ development to be 1.8 years.[3] Although the attenuated vaccine strain has a very high protective ability against varicella, it leads to HZ development in a shorter time. It stimulates the immune system less than the wild-type strain.[27] It is already known that HZ occurs at an earlier age in those who have had a varicella infection before the age of 1 year.[3,6,7] In young children, the immune response to VZV is insufficient, and thus virus reactivation can occur earlier.[29] We consider that the vaccination of varicella at the 12th month also contributes to the development of HZ in early childhood. However, contrary to this hypothesis, Tseng et al.,

comparing children under 12 years old that were vaccinated at 12–18 months and after 5 years of age, found no significant relationship between vaccination age and HZ incidence.[12]

In our study, 93% of children were between the ages of 2 and 10 years in the prevaccination period, and there were no adolescent cases in this group. In contrast, in the postvaccination period, there was a noteworthy increase in the number of cases aged > 10 years. With the vaccination program, the incidence of varicella was reduced through the decreased number of wild-type strains in the environment. In the non-vaccinated children who were exposed to wild-type strains at a later age, the immune response that developed was stronger than in the case of attenuated vaccine strains, thus decreasing the frequency of early HZ in non-vaccinated cases. However, as the decrease in the incidence of varicella continued, there was a further reduction in the number of wild-type strains in the environment, which lowered the exogenous boosting effect and resulted in an increase in HZ through the reactivation of VZV during adolescence. Civen et al. compared the trend of increase in patients with HZ aged under 20 years between 2000–2006 and 2007–2010 and showed that the increase in the HZ incidence in adolescence was less in 2010 than 2006. This relative decrease was attributed to the start of the second dose booster in 2007.[30] In another study conducted in 2018, it was suggested that the universal vaccination program caused a significant increase in the HZ incidence, and vaccination during adolescence could provide a more moderate increase in the rate of HZ.[31] In their modeling study, Wolfson et al. evaluated the cost-effectiveness of the varicella vaccination strategy of Turkey by taking into account varicella and HZ together and reported that two-dose vaccination would be more beneficial, and applying the two doses at short intervals, at 12 and 18 months, would also be more cost-effective.[9]

Our study has some limitations, with the most important being that it was conducted in a single center. Examining the frequency of HZ in children and adolescents admitted to the hospital may have caused the HZ prevalence to be higher than in the general population. On the other hand, considering that HZ manifests with milder symptoms in childhood, fewer hospital referrals may also be expected, which would not reflect the situation in one portion of the society, resulting in seemingly lower HZ prevalence. Furthermore, since our study only covered the first 6 years of routine varicella vaccination, the trend during adolescence could not be evaluated among the vaccinated cases. Investigating the history of varicella disease and antiviral treatment, screening additional conditions, such as immunosuppression and malignancies that could facilitate VZV reactivation, and evaluation of clinical features, such as lesion localization and pain, can provide more accurate results in comparing the HZ frequency and demographic characteristics of patients.

In conclusion, with the implementation of a universal varicella vaccination program in Turkey, there has been a decrease in the HZ prevalence among children and adolescents aged <18 years, but this decline remains below the required level, especially in non-vaccinated individuals. In this study, we observed that with a single dose of varicella vaccination, the development of HZ shifted toward adolescence among non-vaccinated children. At the same time, vaccinated cases began to develop this disease at an earlier age. Long-term studies are required to determine whether the increase in HZ in adolescence will continue in non-vaccinated children, reveal the HZ rate at earlier ages and development of adolescent HZ in vaccinated children, and determine whether HZ development in adults is shifting toward younger ages. Such studies will help determine whether a second-dose booster is required for the varicella vaccine and identify the optimum age for booster vaccine administration.

AUTHOR CONTRIBUTION

Concept: Inan Yuksel Esma, Kara Polat Asude, Gore Karaali Muge, Koku Aksu Ayse Esra. Data collection or processing: Kara Polat Asude, Gore Karaali Muge. Analysis and interpretation: Inan Yuksel Esma, Kara Polat Asude, Gore Karaali Muge, Koku Aksu Ayse Esra, Gurel Mehmet Salih. Literature review: Inan Yuksel Esma, Koku Aksu Ayse Esra.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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