**The association between childhood varicella vaccination and herpes zoster in the pediatric population**

Ester Forer MD (1), Adi Yariv (2), Daniel Ostrovsky B.Med.Sc (2), Amir Horev MD (2, 3)

1. Pediatrics Department, Soroka University Medical Center, Beer Sheva, Israel.
2. Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel.
3. Pediatric Dermatology Service, Soroka University Medical Center, Beer Sheva, Israel.

**Corresponding author:**

Dr. Amir Horev

Head of Pediatric Dermatology, Soroka University Medical Center, Beer Sheva, Israel

Postal address: 151 Yiztchak Rager St., Beer Sheva, Israel

Telephone number: +97286400653

Email address: amirhr@clalit.org.il

Abstract

Varicella zoster is a virus of the family *Herpesviridae* that primarily infects children. One of its secondary manifestations can be herpes zoster, also known as shingles, a dermatological form of clinical significance with potential complications, risks, and related morbidity. Vaccination against the varicella virus has been in use worldwide in recent years, including in the state of Israel. In the present study, we compared herpes zoster incidence before and after implementation of the mandatory vaccine against varicella zoster virus in a large cohort in southern Israel. As a secondary aim, we characterized several parameters, including age, sex, and ethnic sector, among herpes zoster cases and evaluated the complication rate to identify data relevant to the immunization status of the pediatric population. By collecting data on a total of 2895 herpes zoster cases in ecological research, we demonstrated a significant increase in herpes zoster cases in southern Israel following the initiation of mandatory varicella zoster vaccination in 2008, but a decrease in the herpes zoster complication rate. In addition, in a unique Arab population with different cultural structures and customs that is known to be more adherent to vaccination programs in southern Israel, we observed a greater increase in herpes zoster cases compared with the Jewish sector, thereby strengthening the potential of a causal association. In conclusion, we were able to shed light on the association between the varicella zoster vaccine and herpes zoster-related morbidity.

Introduction

Varicella zoster virus (VZV) is a virus of the family *Herpesviridae*. VZV affects only humans, and the clinical manifestations of VZV infection are classified as varicella (chickenpox) or herpes zoster (HZ) (shingles). The virus primarily infects children, manifesting as chickenpox, and is characterized by the cutaneous distribution of diffuse and scattered maculopapular vesicles. VZV then becomes latent in the nervous system. As cellular immunity to the virus diminishes with age or in persons in an immunocompromised state, reactivation of the latent VZV may occur, resulting in shingles, which is characterized by unilateral vesicular eruptions within the affected dermatomes, and possibly shingles-associated complications, including postherpetic neuralgia, ocular involvement, and central nervous system disease [1].

Varicella is considered a self-limiting disease that primarily infects children. In 2014, the World Health Organization (WHO) estimated approximately 4.2 million varicella cases with severe complications and around 4200 related deaths per year worldwide [2]. In France, the disease was associated with severe complications in 3% of patients younger than 15 years of age and in 6% of patients older than 15, including secondary bacterial infections of the skin and lungs, sepsis, aseptic meningitis, encephalitis, and Reye syndrome [3].

A significant decline in varicella incidence has been observed in countries that introduced varicella vaccination. The United States became the first country to implement a routine childhood varicella vaccination program after the vaccine was licensed in 1995 [4]. The Centers for Disease Control (CDC) recommends two doses of the VZV vaccine for children, adolescents, and adults who have never had chickenpox and were never vaccinated. Children are routinely recommended to receive the first dose at 12 to 15 months of age and the second dose at 4 to 6 years of age [5]. In Israel, a mandatory VZV vaccination program was established in 2008, requiring two doses at 1 and 6 years of age.

In December 2014, varicella vaccines were recommended in 33 predominantly higher socioeconomic countries where the vaccination program was not fully implemented, implying that, despite an established effectiveness, many countries still do not routinely vaccinate children against VZV [6]. The reasons for the low adoption rate could include implementation costs, an increased age of onset, which is associated with a clinically severe presentation and may increase the incidence of HZ [7], or concerns regarding the post-vaccination complications in the pediatric population. These complications may range from life-threatening infections caused by the vaccine strain, such as pneumonitis with a generalized varicelliform rash [8] and postherpetic neuralgia and meningoencephalitis with or without rash [9], which are much more common in immunodeficient populations, to dermatological HZ infection, which may affect both immunodeficient [10] and healthy [11] populations.

To shed light on vaccination-related controversies, the primary aim of the present study was to compare HZ incidence before and after the mandatory VZV program was implemented in a large cohort in southern Israel. The secondary aim was to characterize several parameters, including age, sex, and ethnic sector, among HZ cases and to evaluate the rate of HZ complications to derive data relevant to the immunization status of the pediatric population.

Methods

*Study design*

This retrospective ecological study was conducted between 2000 and 2021. The study was approved by the local ethics committee of Soroka University Medical Center (SUMC) (No. SOR-0311-20).

We used secondary analysis to describe the main milestones of VZV vaccination. Three years are known to be particularly important: 1995 is when the VZV vaccine was introduced worldwide, 2001 is when the vaccine arrived in Israel, and 2008 marked the beginning of the mandatory vaccination of children by the state of Israel. To analyze the time series data for VZV incidence, we used a Poisson distribution that was regressed on the years 2001 and 2008. Because 2008 marked the beginning of the mandatory vaccination, it was defined as the main exposure and we thus divided our results into a pre-vaccination period (2001–2007) and post-vaccination period (2008–2021). In addition, adjustment to relevant events was made.

*Study population*

The study population comprised patients aged 0–18 years diagnosed with HZ, either insured within the southern district of Clalit Health Services (CHS) or seen at SUMC. CHS is the largest public health care provider organization in Israel and serves more than half of Israel’s population, covering approximately 4,600,000 people (and over 750,000 people in southern Israel). SUMC, with 1,200 beds, is the sole tertiary hospital in the south of Israel, covering a massive geographical area. The data regarding the study population, including the child's age group upon diagnosis with HZ, sex, and ethnic sector, is presented in Table 1.

The control group comprised general study population data extracted from a digital system called Bina that encompasses information on all children aged 0–18 years who live in Israel's southern district and are insured by the CHS.

Subject confidentiality was maintained throughout the study. To ensure that the data could always be tracked back to the source data, a unique subject identification code was used that allowed the identification of all data reported for each subject. Data relating to the study might be made available to third parties (e.g., in the case of an audit performed by regulatory authorities) provided the data are treated confidentially and the subject’s privacy is guaranteed.

*Statistical analysis*

Data were retrieved from the CHS and SUMC databases. Continuous variables with a normal distribution are presented as mean and standard deviation. Ordinal variables or continuous variables with a non-normal distribution are presented as median and interquartile range (IQR). Categorical variables are presented as counts and percent of the total.

Results

A total of 2895 HZ cases were included in the research period. Between 2000 and 2007, 109.24 HZ cases per 100,000 population per year were documented. A major increase in the incidence rate of infected children was observed from 2008 to 2021, with a total of 354.71 HZ cases per 100,000 population per year (Figure A).

Females were more affected than males between 2000 and 2007, with an average of 78.03 HZ cases per 100,000 population per year versus an average of 44.87 HZ cases per 100,000 population per year among males. In contrast, both females and males were almost identically affected between 2008 and 2021, with an average of 238.33 HZ cases per 100,000 population per year among females versus an average of 239.244 HZ cases per 100,000 population per year among males (Figure B).

An additional subdivision of HZ cases was made according to ethnic sector (Jews and Arabs). Because the Arab population mainly lives in separate villages and towns in the southern Israel district and because the population data have been taken from the community data, where sector is also defined by settlement, a direct association could be made between the number of HZ cases and the two distinct ethnic sectors. Using this division, which is an accepted statistical method for comparing populations in Israel [12], we found that, until 2007, the number of HZ cases was similar in the two ethnic sectors (an average rate of 10.1 cases per 100,000 population for the Jewish sector and of 26.98 cases per 100,000 population for the Arab sector). However, from 2008, a major increase in the number of HZ cases was observed in the Arab sector while a less dominant increase was observed in the Jewish sector (an average rate of 96.56 cases per 100,000 population for the Jewish sector and of 255.24 cases per 100,000 population for the Arab sector) (Figure C).

An additional classification according to age group was conducted for the pre- and post-vaccination periods for both sexes and sectors. The results showed that, in most age groups, a distinct increase in HZ cases occurred in the post-vaccination era. The greatest increase occurred in adolescents aged 12–18 years, with an average increase of 10.51% in HZ cases per 100,000 population in the post-vaccination period compared with the pre-vaccination period (Figure D).

As noted above, 2008 was the year in which mandatory vaccination against VZV was implemented in Israel. Thus, 2007 is a pre-vaccination time, and it has a case number approaching that of the average number in the entire study population. Specifically, 78 HZ cases were documented in 2007, with sex and age characteristics that were similar to those found in the post-vaccination era (female-to-male ratio, 0.9; mean age, 8.9 ± 4.9 years, resembling the sex and age distributions of the patients in the post-vaccination period at 0.97 and 8.9 ± 5.2, respectively). Chi-square testing revealed a significant increase in HZ cases between 2007 and 2008: χ2 = 41.133, df = 1, p-value = 1.422e-10.

Upon comparing both sectors and several age groups, we additionally found that the increase in HZ incidence per 100,000 population among children (both males and females) aged 6 years and older was greater in the Arab sector than in the Jewish sector (an average incidence rate increase of 6.56% for the Jewish sector and of 8.17% for the Arab sector). Before the age of 6 years, there was also a greater increase in the HZ case rate among the Arab population (an average incidence rate increase of 0.63% for the Jewish sector and of 3.43% for the Arab sector) but the trend was not as distinct and comprehensive as the one seen for the older age group (mainly due to the group of Jewish females aged 0–2 years, which showed a decrease of 0.895% in HZ cases per 100,000 population in the post-vaccination period compared with the pre-vaccination period) (Table 1).

Because HZ has several complications [3, 8, 9, 11, 13, 14, 15], our study evaluated complication rates by collecting relevant International Classification of Disease codes and comparing them in the pre- and post-vaccination eras. No complications involving the central nervous system were found in our study population. On the other hand, ophthalmic and dermatological complications were found in the two periods, including HZ keratoconjunctivitis and eyelid dermatitis. Due to the relatively small number of complications and in accordance with the mandatory VZV vaccination program implemented in Israel in 2008, we compared their incidence rates between 2000–2007 and 2008–2021, rather than separately per year. Our results showed that the incidence of complications was significantly higher before 2008 than after 2008 (0.043 versus 0.006 total complications/total cases). The same trend was demonstrated when the complication rates were compared with the general population data (4347.82 versus 575.53 complications per 100,000 population).

Discussion

In the current study, a significant increase in the HZ incidence rate was documented after the varicella vaccine became mandatory in Israel in 2008. We believe that the changes in the number of HZ cases in Israel between 2000 and 2021 may be strongly related to the vaccination program operated by the government, in line with related data from large studies conducted in other countries worldwide. Before the introduction of routine varicella vaccination, the reported HZ incidence rates among children and adolescents around the world ranged from 42 to 220/100,000 person-years [16, 17, 18]. Experts' opinions over the past years have led to research concluding that HZ frequency and severity are less after varicella vaccination than after wild-type varicella infection [13, 14]. During a period with high varicella vaccine coverage (2003–2014), a 72% decrease in overall HZ incidence in children < 18 years of age was reported in a study conducted in the United States, which included a population totaling 199,797 children from multiple health centers [19]. A similar decline in HZ rates after 2006 in children 0–17 years old was demonstrated in the United States by Harpaz et al. [20]. On the other hand, the annual incidences of HZ did not change significantly in children in Turkey, according to a large study investigating a total of 1,090,803 patients, both children and adults, with a time trend analysis of 9 years [21].

Despite the above-mentioned decline in the United States and arrest in Turkey in pediatric HZ cases following VZV vaccination, there are still reports regarding post-vaccination HZ cases. Most are found in immunodeficient populations while some occur in immunocompetent children, either in the same dermatome in which the vaccine was injected or at a remote location. In some of these cases, the zoster rash can be as severe as that following wild-type varicella [11, 15].

To address the question of whether VZV vaccination contributed positively or negatively to HZ-related morbidity, we used four notable findings in our study. First, we consider the year 2007 to be an indicator. We assume that the increase in HZ cases with similar age, sex, and sector characteristics to those of the post-vaccination era, at a time when vaccinations were not yet mandatory but began to be offered to certain populations, suggests a possible correlation between VZV vaccination and HZ occurrence. Second, because the Arab population in the southern Israel district has previously been proven to be more adherent to routine vaccination programs [12], the greater increase in HZ cases in the Arab sector in the post-vaccination era implies a possible correlation between VZV vaccination and HZ occurrence. Third, the fact that the change in the number of HZ cases was most predominantly observed in the older age group (children aged 12–18 years) in the post-vaccination era rather than in the pre-vaccination era is in agreement with the physiology of the disease [22]; because reactivation of the latent VZV is preceded by several years of virus latency in the nerve root ganglia, it is expected that, if vaccination does affect disease rates, it will be most significant in the older age group due to their longer time interval since vaccination to allow reactivation to occur, as was highlighted in our study. Finally, as was biologically proven in the past, wild-type virus strains are correlated with a greater risk of complications [13, 14]. This statement is in line with our finding of a higher HZ dermatological and ophthalmic complication incidence and HZ complication incidence per 100,000 population in the pre-vaccination period. Thus, we assume that the mandatory VZV vaccination program in Israel contributed positively to avoiding severe HZ morbidity and related complications.

Further support to the research hypothesis may be obtained by the observation of differences between children younger and older than 6 years of age: the increase in the incidence of HZ cases was unilaterally demonstrated in the latter group but not observed in the former group. Because the second vaccine dose is given in Israel at the age of 6 years and because adherence to the national vaccination program was found to be greater among Arabs than among Jews [12], it may be possible to assume that the massive live attenuated virus exposure associated with the second dose could be greater in the Arab sector rather than in the Jewish sector and account for the distinct increase in HZ cases in the Arab sector.

Our research has some noteworthy strengths. It included a semi-national database supplied by CHS, the largest health supply service in the southern district, where our study was conducted. The large number of HZ cases documented in the post-VZV vaccination era enabled us to show a clear trend between cases and vaccination. By collecting data regarding both patients who were managed as outpatients only and those who had to be hospitalized due to HZ and its complications, we managed to derive a significant amount of information and decipher its clinically important consequences. An additional advantage of our work that differentiates it from former HZ and VZV vaccination-related studies is that our study population has unique characteristics, namely, that it comprises two ethnic groups. The originality of this study is highlighted by some specific characteristics, such as a known vaccination adherence rate, a nearly single health care provider in the community, and a single regional tertiary hospital that provides some geographic isolation.

The limitations of our study are in part due to the fact that it involves ecological research. Thus, the relationships among variables at a population level may not necessarily be the same as at the individual level. In addition, its retrospective nature limits our ability to address clinical questions that necessitate a direct association.

Conclusion

In the current study, we demonstrated a major increase in HZ cases in south Israel following the initiation of mandatory VZV vaccination in 2008, but a decrease in the HZ complication rate. Further prospective studies are warranted to address this issue and validate our findings.