Children with breakthrough varicella infection requiring hospitalization in Turkey (VARICOMP Study 2008–2013)

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A B S T R A C T

Introduction: Varicella in previously immunized individuals, known as "breakthrough varicella". While the majority of breakthrough cases are mild, some may be severe, requiring hospitalization in previously healthy children or children with an underlying condition.

Methods: This report, as a part of the prospective national pediatric varicella hospitalizations study (including 29 centers, represent 50% of pediatric population) in Turkey, is aimed to evaluate breakthrough varicella infection requiring hospitalization before the routine use of single-dose live varicella vaccine in national program from 2008 to 2013 (<10% of the pediatric age group received a single-dose vaccine).

Results: In the time period, 1939 children were hospitalized due to varicella infection in Turkey; 36 children (20 boys, 16 girls, mean age 68.0±37.6 months, all received single dose live varicella vaccine) with breakthrough varicella infection might be severe in previously healthy children (61.1%) and children with immune-compromising conditions (38.9%). The time elapsed between vaccination and hospitalization was approximately 5 years, and neurological complications, mainly encephalitis and meningitis, were the most common reason for hospitalization in previously healthy children.

Conclusion: Pediatric breakthrough varicella requiring hospitalization have been seen in Turkey, is mainly observed in previously healthy children at 5 years after a single-dose varicella vaccine. The varicella vaccine has been implemented as part of the National Immunization Program in Turkey in 2013 (a single dose at age 12 months). Further surveillance in the same settings could evaluate the effectiveness of national immunization with single-dose varicella vaccine at 12 months of age and potential need for second dose of vaccine.

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Varicella in previously immunized individuals, known as “breakthrough varicella”, is usually a mild and self-limiting condition. Breakthrough varicella infection has been defined as any varicella-zoster virus infection occurring over 42 days after vaccination [1]. While the majority of breakthrough cases are mild, some may be more severe, requiring hospitalization in previously healthy children or children with an underlying condition [2]. In Turkey, single-dose live varicella vaccine was introduced into the National Immunization Program in February 2013. Before this implementation, varicella vaccine had been available privately and <10% of children were vaccinated. The VARICOMP Study is a multi-center study, conducted to provide data on hospitalization for varicella infections in a pediatric population in Turkey for the 5 years between 2008 and 2013 (pre-vaccine era) and 2013 and 2018 (with routine use of single-dose live varicella vaccine). In this report, as a part of the prospective national pediatric varicella hospitalization study (VARICOMP) in Turkey, it is aimed to evaluate breakthrough varicella infection requiring hospitalization in the pre-vaccine era, between 2008 and 2013.

1. Material and methods

This is the first part of the VARICOMP multi-center study, which was conducted to provide data on hospitalization for varicella infections in a pediatric population in Turkey for the 5 years between 2008 and 2013 (ClinicalTrials.gov Identifier: NCT01887496). During this time period, the live attenuated varicella vaccine was licensed in Turkey but was only occasionally used in private practice (<10% of the pediatric population) and had not yet been introduced into the national immunization program. Parents were required to pay for the immunization of their children. Compulsory health insurance covers 100% of the population between 0 and 18 years of age, and the government is the main provider of health expenditure. The reporting of varicella infections is not mandatory in Turkey, and there is no official registration system using ICD code data to track inpatient or outpatient cases. For this study, official invitations to participate were sent to the pediatric departments of 29 hospitals in 14 cities (50% of the entire population) [3]. All participating centers reviewed their medical records to identify patients under 18 years of age between 2008 and 2013 (until February 2013, the introduction date of single-dose live varicella vaccine). Diagnosis at discharge was used as the main criterion for inclusion because of a previous study indicating that discharge data provided a valid measurement of varicella-related hospitalization [4]. Cases were identified by the International Classification of Disease, Tenth Revision (ICD-10) diagnostic codes for chickenpox infection or chickenpox-associated complications, if available. Previously healthy children and children with underlying conditions, such as immunosuppression or chronic disease were enrolled. The primary goal of this part of the VARICOMP study was to evaluate breakthrough varicella infection requiring hospitalization. Breakthrough varicella infection was defined as any varicella-zoster virus infection occurring over 42 days after vaccination.

Details of admission time, gender, age, receipt of varicella vaccine, time elapsed since vaccination, underlying conditions, reason for admission, nature and type of any varicella-associated complications, and presence of varicella serology were noted. Data indicating the length of hospital stay, intensive care unit stay, use of mechanical ventilation, administration of acyclovir (dose and duration if available), administration of intravenous immunoglobulin (dose and duration if available), antibiotic therapy and hospitalization outcome (survival to hospital discharge, sequelae at hospital discharge or death) were also collected.

2. Statistical analysis

Statistical analyses were performed using SPSS version 16.0 for personal computers (Chicago, IL, USA). Chi-squared tests were used to compare categorical data, and t-tests were used to compare normally distributed continuous data. A value of p < 0.05 was considered statistically significant.

3. Results

A total of 29 health care centers (including university hospitals, maternity and children's hospitals and state hospitals) agreed to participate in the VARICOMP study and these centers included 50% of the pediatric population in the pre-varicella vaccine era in Turkey. In the time period of October 2008–October 2013, 1939 children were hospitalized due to varicella infection in Turkey, of whom 36 had breakthrough varicella infection. All of these 36 children (20 males, 16 females) had received single-dose live varicella vaccine. The mean age was 68.0 ± 37.6 months (range, 18–181 months). Underlying disease was determined in 14 children (38.9%), 10 out of them were healthy receiving the varicella vaccine (acute lymphoblastic leukemia (n = 6), rhabdomyosarcoma (n = 1), pons glioma (n = 1), hemophagocytic lymphohistiocytosis (n = 1), polymyositis (n = 1)) and 4 out of them have been diagnosed as epilepsy (n = 3) and diabetes mellitus (n = 1) prior the immunization. In 61.1% (n = 22) of reported children, no underlying condition was determined. None of children who have epilepsy have neurological findings at admission and follow-up period. The mean time since vaccination was 56.0 ± 37.6 months (range, 6–169 months).

The cause of hospitalization was neurological complications in 12 children (33.3%) (2 febrile seizure, 1 cerebellitis, 9 encephalitis/meningitis), secondary bacterial infections in 5 (4 skin and skin structure infections, 1 S. aureus sepsis), fever in 4, pneumonia in 4, hematological complications in 4 (1 febrile neutropenia, 2 thrombocytopenia, 1 neutropenia), feeding difficulties in 4 (oral lesions, dehydration), disseminated varicella in 3, severe eye involvement in 1 and underlying immunocompromised condition in 7. Intensive care unit admittance was required by 2 children and none required mechanical ventilation. The median length of hospital stay related to varicella infection was 8 days (3–23 days). Acyclovir was administered to 30 children (83.3%) (median use: 8 days), antibiotics to 24 children (70.6%), and intravenous immunoglobulin to 2 children. One child with hematological-oncological malignancy died due to varicella-related complications such as secondary bacterial infections and sepsis (Table 1).

When children with underlying conditions were compared with previously healthy children, age, gender distribution, time since vaccination and varicella-related complications, except for neurological complications, acyclovir use, antibiotic use and IVIG use were similar (p > 0.05). Neurological complications were determined as a common cause of hospitalization in previously healthy children compared to children with underlying conditions (12/22 children vs. 2/14 children; p < 0.05), with the majority of cases having meningitis/meningoencephalitis (9/22 children vs. 0/22 children; p < 0.01). The length of hospital stay was longer in children with an underlying condition (10.0 ± 4.7 days vs. 7.0 ± 2.7 days; p < 0.05).

4. Discussion

Breakthrough varicella infection may be severe both in previously healthy children and children with immune-compromising conditions. This study reports 36 children with breakthrough varicella infection requiring hospitalization during the 5-year pre-vaccine period in Turkey (<10% of the pediatric age group received
Table 1
Demographic and clinical findings of the children requiring hospitalization due to breakthrough varicella infection.

<table>
<thead>
<tr>
<th></th>
<th>Previously healthy children (n = 22)</th>
<th>Presence of underlying disease (n = 14)</th>
<th>Total (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>65.6 ± 41.8</td>
<td>71.8 ± 30.8</td>
<td>68.0 ± 37.6</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/10</td>
<td>8/6</td>
<td>20/16</td>
</tr>
<tr>
<td>Time since vaccination (months)</td>
<td>53.5 ± 41.8</td>
<td>59.8 ± 41.8</td>
<td>56.0 ± 37.6</td>
</tr>
<tr>
<td>Severe varicella</td>
<td>2 (9%)</td>
<td>1 (7.1%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Due to underlying condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever and dehydration</td>
<td>5/22 (22.7%)</td>
<td>3/21 (14.6%)</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>3 (13.6%)</td>
<td>1 (7.1%)</td>
<td>5 (13.8%)</td>
</tr>
<tr>
<td>Severe eye involvement</td>
<td>1/2 (4.5%)</td>
<td>–</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Hematological complications</td>
<td></td>
<td>2 (14.3%)</td>
<td>2 (5.5%)</td>
</tr>
<tr>
<td>Secondary bacterial infections</td>
<td>3 (13.6%)</td>
<td>2 (14.3%)</td>
<td>5 (13.8%)</td>
</tr>
<tr>
<td>Skin and skin structure infections</td>
<td>1 (4.5%)</td>
<td>–</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>12/54.5%</td>
<td>2 (14.2%)</td>
<td>12 (33.3%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>2/22 (9%)</td>
<td>2/14 (14.2%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Cerebellitis</td>
<td>1/22 (4.5%)</td>
<td>–</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Meningitis/Encephalitis</td>
<td>9/22 (40.9%)</td>
<td>–</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Intensive care unit stay</td>
<td>3 (13.6%)</td>
<td>4 (28.5%)</td>
<td>7 (19.4%)</td>
</tr>
<tr>
<td>Requiring mechanical ventilation</td>
<td></td>
<td>1 (7.1%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Acyclovir use</td>
<td>17 (77.2%)</td>
<td>13 (92.8%)</td>
<td>30 (83.3%)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>16 (72.7%)</td>
<td>8 (57.1%)</td>
<td>24 (66.6%)</td>
</tr>
<tr>
<td>IVIG use</td>
<td>1 (4.5%)</td>
<td>1 (7.1%)</td>
<td>2 (5.5%)</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>7.0 ± 2.7</td>
<td>10.0 ± 4.7*</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>–</td>
<td>1 (7.1%)</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>

\[ p < 0.05. \]
\[ p < 0.01. \]

A single-dose vaccine). The time elapsed since vaccination was approximately 5 years, and neurological complications, mainly encephalitis and meningitis, were the most common reason for hospitalization in previously healthy children.

Breakthrough infections in children, who have been vaccinated with varicella vaccine, have been reported to occur at a slightly higher frequency than those in subjects vaccinated with other live vaccines. Published data represent an approximate average of 75–88% vaccine effectiveness for one dose of varicella vaccine for all types of varicella and an approximate vaccine failure rate of 20% [5]. Effectiveness against severe/moderate disease was higher (95–100%) than for disease of any severity. In non-outbreak situation studies, the breakthrough infection rate varies widely, ranging from 2.1% to 9.5% [6,7]. In Turkey, Kurugol et al. [8] showed that 27.7% of children developed breakthrough infection from a total of 1683 vaccinated children and 24.7% of those had a moderate to severe disease course. In Taiwan, between 2000 and 2007, of more than 1 million children who received single-dose varicella vaccine, 2% had breakthrough infections and 0.016% required hospitalization and the overall vaccine effectiveness against varicella-related hospitalization was 85.4%. The authors explained the higher rate of hospitalization (lower vaccine efficacy compared with Western countries) with the ease of access to hospitalization [7]. Chaves et al. [9] reported that although cases of breakthrough varicella disease were 13 times less likely to cause moderate or severe illness, patients were almost three times more likely to be seen by a physician. In the current series, only 3 children were hospitalized due to the severity of the rash, and the remaining cases were hospitalized due to systemic complications. In Turkey, single-dose live varicella vaccine was introduced into the NIP in March 2013, and the study cases presented here originate from the pre-vaccine era when the vaccine was only available privately. From these results, it is not possible to estimate the vaccine efficacy, although severe cases requiring hospitalization might be explained by higher rates of natural infection during childhood. Most studies have shown that the efficacy of single-dose varicella vaccine might be lower during varicella outbreaks [2,10]. The reporting of varicella infections is not mandatory in Turkey, and there is no official registration system using ICD code data to track inpatient or outpatient cases. Therefore, it is difficult to explain the outbreaks. An increased risk for breakthrough disease has been noted with decreasing age at vaccination, time elapsed since vaccination, history of asthma, corticosteroid use, vaccination with varicella vaccine within 30 days of live attenuated measles–mumps and varicella vaccine [8]. While these associations have not been consistently reproduced in all studies, primary vaccine failure is evidently common in healthy young children after a single dose of live attenuated varicella vaccine and the most plausible explanation is that some immunized children do not develop humoral immunity to the varicella virus [11]. Across all studies 0–24% of subjects have been observed to fail to seroconvert after primary vaccination, depending on the age group, vaccine titer and vaccine lot. In previous studies, primary vaccine failure has been commonly seen in children one year after the first dose. In the current study, the time elapsed since vaccination was determined as 56.0 ± 37.6 months. In contrast to previous studies, the breakthrough cases requiring hospitalization in the current study were generally older than 4 years. In the 29 publications that have reported on breakthrough varicella rates with time, an increased risk of breakthrough varicella has been shown with time and this increased risk has generally been observed around 4–5 years post-vaccination [5]. A large retrospective study of over 11,000 children found that the time since vaccination is an important risk factor for breakthrough varicella, with both incidence and severity increasing over a 10-year period [8]. Galil et al. [12] reported that children who had been vaccinated for more than three years were at a two-fold greater risk of varicella infection than those who had been vaccinated for shorter periods of time. In a 10-year follow-up study, Chaves et al. [9] reported that children who had been vaccinated for more than 5 years were at 2.6 times greater risk of acquiring moderate to severe varicella than those who had been vaccinated for a shorter time. The annual rate of breakthrough varicella significantly increased with the time
since vaccination, from 1.6 cases per 1000 person-years within 1 year after vaccination to 9.0 per 1000 person-years at 5 years and 58.2 per 1000 person-years at 9 years. In Turkey, Kurugol et al. [8] reported that the median age at vaccination was 13 months and the median time elapsed since vaccination was 72 months for breakthrough infection. The frequency of breakthrough infection was significantly higher (3.7-fold higher risk for breakthrough infection) in children vaccinated more than 5 years previously than in children who had been vaccinated <5 years and the rate of breakthrough infection was 29.6% at 8 years after vaccination and 63% at 10 years after vaccination. The increased risk of breakthrough infection is presumably a result of diminished immunity in some vaccinated children over time. In the current study, the time elapsed since vaccination was approximately 5 years. In our case series, 40% of children have an underlying condition, and 75% of these cases which have an immunocompromised condition are healthy during the immunization. Immunocompromised condition including childhood malignancies might be result with an antibody deficiency and severe courses. 42.8% of these cases (who have underlying condition) have been hospitalized mainly due to underlying disease. Two case-control studies from the United States and China showed a drop after the first year after the first dose and then rates remained stable [5]. Long-term studies have not indicated significant waning immunity after varicella vaccination, as they have shown that there is no increase in breakthrough varicella between 4 and 8 years after vaccination. It should be emphasized that the results of long-term studies can be difficult to evaluate in areas where wild-type virus still circulates, as this can provide a natural boost to the immune system, reducing secondary vaccine failure [5]. In the study by Kurugol et al. [8], it was suggested that breakthrough varicella is frequent in an environment in which primary varicella infections are common in Turkey. Vaccination at younger than 15 months, and the presence of asthma or eczema were not related with an increased risk of breakthrough infection. The current study included a time period when the varicella vaccine was not a part of the national immunization program. The higher rate observed in Turkey and severe cases requiring hospitalization might be related to most of the vaccinated children having been exposed to the wild-type varicella virus.

Previous studies have reported that children admitted to hospitals with breakthrough infection have a moderate to severe level of the disease with up to more than 300 lesions. Children aged between 8 and 14 years of age have a higher incidence of moderate to severe disease compared to children aged 1–7 years [9]. Diarrhea, skin infections, otitis media, and pharyngitis are the reported causes of admission. Other, rare complications include pneumonia, hemorrhagic complications, viral meningitis, and septicemia. In the current study, the majority of the reported cases were hospitalized for neurological reasons, mainly meningitis/encephalitis in previously healthy children. There have been sporadic cases reports about neurological disorders associated with breakthrough varicella infection, such as transverse myelitis [13]. One of the reported cases was of encephalitis in an otherwise healthy 4-year-old child who received varicella vaccination at 3 years of age. The current study series is the largest series including meningitis/encephalitis associated with breakthrough infection. One of the current series patients with leukemia died due to secondary bacterial infections and sepsis related to the breakthrough varicella infection. While the majority of neurological complications occurred in previously healthy children, the length of hospital stay, acyclovir-antibiotic and IVIG use were similar between the previously healthy children and those with an underlying condition.

During the prevaccine period, <10% of children have been vaccinated with single-dose varicella vaccine, and the price of the vaccine have been paid by the parents. These children might have a higher socioeconomic status comparing the children without vaccinated, and these socioeconomic differences and potential better access to health care might affect the disease course. Also children who have underlying condition might have low threshold to attend the hospital and requiring the hospitalization and this might be effect the difference between the children with or without underlying condition.

The varicella vaccine has been implemented as part of the National Immunization Program in Turkey in 2013 (a single dose at age 12 months). Since the beginning of 2000, the varicella vaccine has been available through private practitioners in Turkey, but the estimated coverage has been less than 10%. Pediatric breakthrough varicella requiring hospitalization is not rare in Turkey, is mainly observed in previously healthy children at 5 years after a single-dose varicella vaccine. Further surveillance in the same settings could evaluate the effectiveness of national immunization with single-dose varicella vaccine at 12 months of age. In the United States, it has been suggested that high antibody titers are required for optimal protection against varicella, rather than seroconversion per se, and that 2 doses are required to achieve this [2]. All published evidence for varicella vaccine failure strongly supports a 2-dose schedule in order to achieve effective control of the disease. Further surveillance in the same settings could evaluate the effectiveness of national immunization with single-dose varicella vaccine at 12 months of age and potential need for second dose of vaccine.

Conflict of interest

Authors declare no conflict of interest for the preparation, writing and publication of this article.

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References