

Complications of varicella infection in children in southern Taiwan

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Background and Purpose: This study was designed to compare the change in complications of varicella infection in children requiring hospitalization before and after varicella vaccine introduction at a tertiary care hospital in southern Taiwan.

Methods: Based on the results of a retrospective study conducted in the pre-vaccine era (1988-1998), a second study was carried out from 1998-2004 (post-vaccine era). In children admitted for varicella-related complications, demographic data, clinical features, microbiological findings, and outcomes were recorded and compared between the two eras.

Results: A decreased annual rate of hospitalization was observed between the two eras. Age-specific hospitalization rates significantly declined in the age group of 1-10 years after vaccine introduction. Secondary skin or soft tissue infections were the most common complications in both periods (pre-vaccine era, 44.1%; post-vaccine era, 56.6%). In the post-vaccine era, 23 (52%) patients had positive bacterial isolates, including 19 *Staphylococcus aureus* (12 oxacillin-sensitive, 7 oxacillin-resistant) and 4 coagulase-negative staphylococci; a higher rate of pneumonitis and lower rate of central nervous system involvement were also observed. No differences were observed in other complications between the two eras. In the post-vaccine era, hematological diseases were the most common underlying conditions (17/18, 94%). The case-fatality rate in the post-vaccine era (1.3%) was similar to that in the pre-vaccine era (2.2%).

Conclusions: A universal childhood varicella vaccination program would ultimately prevent the spread and potential complications of varicella. The result of this study may serve as baseline information as the national vaccination program begins.

Key words: Chickenpox, chickenpox vaccine, hospitalization, morbidity, *Staphylococcus aureus*

Introduction

Varicella is a common contagious disease caused by primary varicella-zoster virus infection. Although it is typically a mild disease, varicella can cause severe illness and death, even in healthy individuals [1,2]. Potentially life-threatening complications include pneumonitis, secondary bacterial infections, encephalitis, and hemorrhage. A live attenuated varicella vaccine was developed in Japan in 1974. It could prevent most of the morbidity caused by varicella in children [3], and

was made commercially available in Taiwan in September 1997. However, until 2004, varicella vaccination was not included as part of routine immunization in all practices of child care. The aim of this hospital-based study was to examine the severity of complications and the varicella-related morbidity and mortality in children before and after the vaccine was introduced in Taiwan, in order to provide a basis for national immunization recommendation.

Methods

The study period was divided into two — June 1988 May 1998 (pre-vaccine era) [4] and June 1998 December 2004 (post-vaccine era). The initial retrospective study

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that was conducted from June 1988 to May 1998 included 136 patients. On the basis of the results, a second study was carried out from June 1998 to December 2004. Patients below 18 years of age who had been admitted for varicella-related complications at a tertiary care hospital during the study period were enrolled. The demographic data and clinical outcome were recorded. Comparisons were made between data obtained from these patients and historical data for varicella patients from 1988 to 1998 [4].

Children were categorized as immunocompromised if they had received cytotoxic chemotherapy or long-term (>2 weeks) corticosteroid therapy, or were less than 28 days old. Varicella-related complication was defined as a condition or event occurring within 14 days of onset of varicella that may have been influenced by varicella-zoster virus infection [5]. The presence of skin and soft tissue bacterial infections was established by clinical findings or confirmed by bacterial cultures. Central nervous system (CNS) dysfunction was defined as documentation of any abnormal neurological examination results. Cerebellar involvement was defined as the presence of ataxia, nystagmus, nausea, and vomiting or nuchal rigidity in various combinations. Meningoencephalitis was defined as the presence of CNS symptoms, sterile cerebrospinal fluid (CSF) and pleocytosis (white blood cell >5/mm³). Encephalopathy was defined as an altered mental status with normal CSF analysis. Pneumonitis was diagnosed when interstitial infiltration or nodular lesion was presented on chest roentgenography, with or without clinical evidence of respiratory distress. Thrombocytopenia was defined as a platelet count below 100,000/mm³. Hepatic involvement was defined as the twofold or higher elevation of serum alanine aminotransferase level.

The annual rate of varicella-related hospitalization was expressed per 1000 hospital admissions. We compared the two periods to assess differences in varicella-related complications before and after the introduction of the vaccine. We also determined the number of varicella vaccinations carried out since 1998 from the hospital records; the varicella vaccine was introduced in our hospital in 1998. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 11.5; SPSS Chicago, IL, USA) software. Chi-squared and Fisher's exact test were used in the analysis, as appropriate. Differences were considered significant at a value of $p < 0.05$.

Results

A total of 76 children treated for varicella complications were included in this study. The mean age was 4.4 ± 3.7 years (range, 2 months to 17 years), with a male predominance (1.3:1) [Table 1]. The mean hospital stay was 6.3 ± 4.0 days (range, 3 to 27 days), which was longer than that in the pre-vaccine era (4.9 ± 2.4 days) [$p = 0.002$]. Overall, 76% (58/76) of the patients were healthy before the onset of varicella and 24% of the patients were immunocompromised. Similar to the results obtained in a study carried out in the pre-vaccine era, secondary skin or soft tissue infections remained the most common complication (56.6%), followed by pneumonitis (30.3%), liver function impairment (13.2%), CNS involvement (9.2%), thrombocytopenia (9.2%), and febrile convulsion (6.6%). As compared with the results of a previous study in the pre-vaccine era [4], a higher rate of pneumonitis ($p = 0.05$) and a lower rate of CNS involvement ($p = 0.01$) were observed. Pneumonitis was by far the most common complication of varicella infection in immunocompromised patients in the post-vaccine era, followed by hepatitis and thrombocytopenia (Table 2).

Among the 43 patients with secondary skin or soft tissue infection, 23 (52%) had positive bacterial isolates, including 12 methicillin-sensitive *S. aureus*, 7 methicillin-resistant *S. aureus*, and 4 coagulase-negative staphylococci.

Varicella outbreaks occurred year-round in southern Taiwan. Notably, there was a downward trend in the annual rate of varicella-related hospitalizations per 1000 admissions after vaccine introduction (Fig. 1). The rate declined from 6.8 in the pre-vaccine era to 3.4 per 1000 admissions in the post-vaccine era. Moreover, the downward trend was more significant with the increase in the number of annual vaccinations (Fig. 1). Average age-specific hospitalization rates declined in all age groups after vaccine introduction, except in the age group of 14-18 years (Table 3).

The majority of children (96.1%) recovered uneventfully. Two children with acute or chronic neurological complications had prolonged convalescence. One patient had cerebellar involvement, and one patient had meningoencephalitis and received anticonvulsants for seizure control. One patient died of pneumonitis, disseminated intravascular coagulation, hepatitis, and acute renal failure. This acute lymphoblastic leukemia patient received cytotoxic chemotherapy prior to the development of varicella. The case-fatality rate in

Table 1. Demographic data and complications of varicella infection before and after vaccine introduction

Characteristic	Pre-vaccine ^a era	Post-vaccine era	<i>p</i>
	1988-1998 (n = 136) No. (%)	1998-2004 (n = 76) No. (%)	
Male/female ratio	1.7:1	1.3:1	0.44
Mean age (years; SD)	3.5 ± 2.8	4.4 ± 3.7	0.09
Mortality	3 (2.2)	1 (1.3)	0.63
Mean hospital stay (days; SD)	4.9 ± 2.4	6.3 ± 4.0	0.002
Complications ^b			
Skin and/or soft tissue bacterial infection	60 (44.1)	43 (56.6)	0.08
Superficial infection only	46 (33.8)	27 (35.5)	
Superficial infection with conjunctivitis	14 (10.3)	6 (7.9)	
Cellulitis	10 (7.4)	9 (11.8)	
Pyomyositis	3 (2.2)	1 (1.3)	
Superficial infection with blepharitis	2 (1.5)	0 (0)	
Arthritis/osteomyelitis	1 (0.7)	1 (1.3)	0.68
CNS dysfunction	31 (22.8)	7 (9.2)	0.01
Cerebellar ataxia	13 (9.6)	2 (2.6)	
Encephalopathy	10 (7.4)	5 (6.6)	
Meningoencephalitis	6 (4.4)	3 (3.9)	
Reye's syndrome	2 (1.5)	0 (0)	
Pneumonitis	25 (18.4)	23 (30.3)	0.05
Thrombocytopenia	16 (11.8)	7 (9.2)	0.57
Hepatitis	14 (10.3)	10 (13.2)	0.53
Febrile convulsion	6 (4.4)	5 (6.6)	0.75
Immunocompromised host infection	23 (16.9)	18 (23.7)	0.23

Abbreviations: SD = standard deviation; CNS = central nervous system

^aData adapted from Tseng et al [4].

^bSome patients had more than one complication.

the post-vaccine era was 1.3% (1/76) which was lower than that in the pre-vaccine era, although the difference was not statistically significant ($p=0.63$).

Discussion

This retrospective comparative study documented a downward trend in varicella-related hospitalizations with the introduction of the varicella vaccine. This finding of a significant reduction in varicella-related hospitalizations highlights a major benefit of varicella vaccine and reinforces the importance of universal varicella vaccination in children.

Generally, after the introduction of vaccines, the annual rates of varicella-related hospitalizations per 1000 admissions were still about 1% in the age group of 14-18 years. Although no statistical significance was observed, the peak trends moved toward the older age groups. Especially, there was a shift in age of case patients towards those who were >13 years of age in the post-vaccine period. Similar results were also found in other countries and northern Taiwan [6-9]. With the introduction

of an effective childhood vaccination program, cases are expected to decline among both children and adults. However, according to the study results, the number of infection cases declined to a greater extent in young children, the age group targeted for vaccination. Our data may emphasize the necessity to extend the vaccination program to the adult group. Besides, in our study, there was also a decline in the rates of varicella-related hospitalizations in infants who are not eligible for vaccination. We assume that the reduction in the rates of varicella infections in this group is solely due to herd-immunity effects [10] or because of the lower severity of the outbreaks than previously recorded. Therefore, further studies are required to analyze the vaccination rates in different age groups and to compare the changes in immunity before and after vaccination.

In both study periods, immunocompromised conditions such as malignancies with cytotoxic chemotherapy and nephrotic syndrome with long-term corticosteroid treatment contributed substantially to varicella-related complications. Moreover, the only patient who died during this study period was also an

Table 2. Complications of varicella infection in immunocompromised patients before and after vaccine introduction

Complication	Pre-vaccine ^a era	Post-vaccine era
	1988-1998 (n = 23)	1998-2004 (n = 18)
	No. (%)	No. (%)
Skin and/or soft tissue bacterial infection	3 (13.0)	1 (5.6)
Superficial infection only	2 (8.7)	1 (5.6)
Superficial infection with conjunctivitis	0 (0)	0 (0)
Cellulitis	1 (4.3)	0 (0)
Pyomyositis	0 (0)	0 (0)
Superficial infection with blepharitis	0 (0)	0 (0)
Arthritis/osteomyelitis	0 (0)	0 (0)
CNS dysfunction	1 (4.3)	1 (5.6)
Cerebellar ataxia	0 (0)	0 (0)
Encephalopathy	0 (0)	0 (0)
Meningoencephalitis	1 (4.3)	1 (5.6)
Reye's syndrome	0 (0)	0 (0)
Pneumonitis	2 (8.7)	7 (38.9)
Thrombocytopenia	3 (13.0)	4 (22.2)
Hepatitis	2 (8.7)	5 (27.8)
Febrile convulsion	0 (0)	0 (0)

Abbreviation: CNS = central nervous system

^aData adapted from Tseng et al [4].

immunocompromised host. In the post-vaccine era, the severity of varicella-related complications was found to decline in normal healthy children. However, in immunocompromised patients, varicella still leads to the development of much more severe conditions than in healthy children. Furthermore, in a previous study, varicella vaccination was found to protect leukemic children against severe varicella infection with an efficacy

approaching 100%, and significantly lowered the contraction rate of zoster from 15% to 3% [11]. Our results support the need for increased awareness of current varicella prevention recommendations among immunocompromised individuals, which includes the targeting of susceptible household contacts for vaccination.

As compared with the pre-vaccine era, secondary bacterial infections of the skin and soft tissue are still

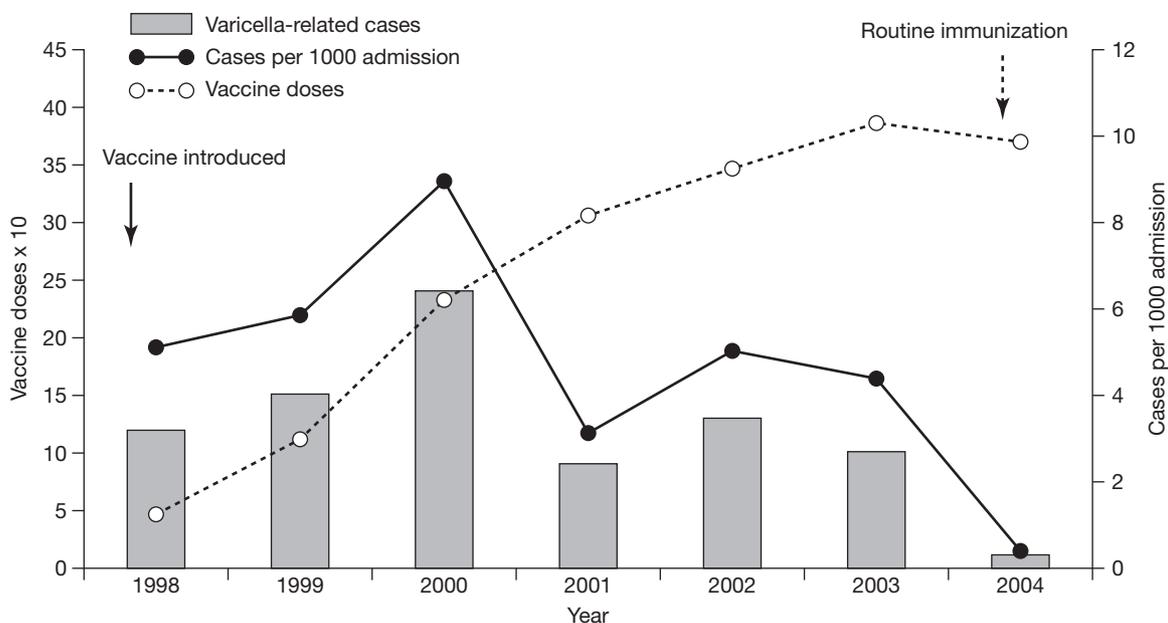


Fig. 1. Varicella-related complications, annual rates of hospitalizations due to varicella per 1000 admissions, and vaccination doses used, 1998-2004

Table 3. Cases and rates (per 1000 admissions) of age-specific varicella-related hospitalization before and after vaccine introduction

Age (years)	Pre-vaccine era (1988-1998) No. of cases (rate)	Post-vaccine era (1998-2004) No. of cases (rate)	<i>p</i>
<1	19 (1.94)	5 (0.58)	0.01
1-4	73 (12.60)	42 (4.88)	<0.001
5-9	27 (10.81)	17 (5.10)	0.01
10-14	17 (9.80)	8 (4.82)	0.09
14-18	0 (0)	4 (9.43)	0.3
Total	136 (6.79)	76 (3.35)	<0.001

the most common infectious complication of varicella in children; similar to that in the pre-vaccine era, *S. aureus* is the most common offending organism. However, in the post-vaccine period, a higher rate of pneumonitis and a lower rate of CNS complication are found. Varicella pneumonitis was once considered rare, but the reported incidence has increased, largely because of greater awareness [12]. Varicella-related pneumonitis was the most common complication in immunocompromised patients in the post-vaccine era and was attributable to the death of one immunocompromised patient in our study. Therefore, in the post-vaccine era, it will become more important to recognize that varicella pneumonitis would be much more severe in immunocompromised patients and to reveal pneumonitis as early as possible and take appropriate treatment. On the other hand, Meyer et al, found that varicella-related CNS complications were more common among children who were <15 years of age than among previously healthy adult decedents [13]. In this study, a decline in CNS complications was observed in the post-vaccine era. The major decline in CNS involvement in the decedents may be attributed primarily to the introduction of vaccine during the past years.

A decline in varicella-related complications and hospitalizations were also found in southern Taiwan after vaccine introduction. Data from 3 varicella active surveillance sites in the United States showed that cases of varicella declined after vaccine implementation, with a substantial reduction beginning 5 years later [6]. This study also documented fewer varicella-related hospitalizations since the vaccine was introduced as routine scheduled vaccination in 2004 (Fig. 1). However, although there was a decline in the number of hospitalizations, potentially preventable varicella-related complications and deaths continued to occur, particularly in immunocompromised patients. In Taiwan, to prevent further complications and deaths, vaccination

efforts should not only target those aged 12 to 24 months [14], but also address catch-up immunization for older children who lack immunity against varicella and the household contacts of immunocompromised patients. The decline in varicella-related hospitalizations observed in this study may serve as baseline information as the national routine vaccination program begins.

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