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**Original Article**

# Disease burden and epidemiological characteristics of varicella in Taiwan from 2000 to 2005

**Yung-Hsiu Lin[1,2], Li-Min Huang[1,2], I-Shou Chang[2,3], Fang-Yu Tsai[2,3], Luan-Yin Chang[1,2]**

*[1]Division of Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei; [2]Varicella-Zoster Working Group, Advisory Committee on Immunization Practices, Taipei, and [3]Department of Biomedical Informatics, National Health Research Institute, Miaoli, Taiwan*

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**Background and purpose:** Varicella has an important impact on public health, especially before the introduction of the varicella vaccine. This study investigated the epidemiological characteristics and disease burden of varicella during the introduction of the varicella vaccine for mass vaccination in Taiwan.

**Methods:** The *International Classification of Diseases, 9th Revision, Clinical Modification* codes related to varicella (052, 052.1, 052.2, 052.7, 052.8, 052.9) were analyzed for the population of Taiwan from 2000 to 2005 through the National Health Insurance database.

**Results:** Most of the patients with varicella were younger than 10 years. The overall age-specific annual incidence peaked in 4- and 5-year-old children (60.5 and 60.2/1000 children, respectively). A significant decrease in incidence among 3- to 6-year-old children was observed in areas with free varicella vaccination ($p<0.001$). Winter was the season for epidemic varicella, particularly January. The varicella-related hospital admission rate was 60/1000 patients (95% confidence interval [CI], 48.5-71.5/1000 patients). Infants younger than 1 year, and adults aged from 19 to 38 years and older than 75 years had the highest hospital admission rates. The mean duration of hospital stay was 5.05 days (95%CI, 4.98-5.12 days). The complication rate among patients admitted to hospital was 39.1%, and the most common complication was lower respiratory tract infection (22.1% among patients admitted to hospital). Twenty nine patients with varicella died; 52% had underlying disease and 72% had complications related to varicella. The annual varicella-related medical expense was highest in 2000 (NT$118.6 million/year) and declined after 2002.

**Conclusions:** Most patients with varicella were younger than 10 years, and the incidence peaked among children aged 4 to 5 years. The incidence of varicella among 3- to 6-year-old children was significantly lower in the areas with a free public vaccination policy. The hospital admission rates were highest for infants and elderly people.

**Key words:** Chickenpox; Epidemiology; Herpesvirus 3, human; Incidence; Primary prevention; Taiwan

## Introduction

Varicella (chickenpox) is the primary disease caused by the varicella zoster virus (VZV). The infection is both common and highly contagious, and has an important health impact for children. Although the clinical course of varicella is usually mild and self-limiting, varicella can cause complications and mortality resulting in financial expense [1-3]. Chickenpox is now considered to be one of the most common vaccine-preventable diseases in many countries [4-7].

Up to 2004, some areas of Taiwan, including Taipei City, Taichung City, and Taichung County, gave free varicella vaccination to 1- to 2-year-old children. Taipei City started the free varicella vaccination program in 1998, and Taichung City and Taichung County gave free varicella vaccination from 1999. Other areas in Taiwan did not provide free varicella vaccination but people could pay for private varicella vaccination. In 2004, a mass varicella immunization program was

*Corresponding author: Dr. Luan-Yin Chang, Division of Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.*
*E-mail: lychang@ntu.edu.tw; ly7077@tpts6.seed.net.tw*

 

established to provide free vaccination for all 1- to 2-year-old children throughout Taiwan.

Since the implementation of National Health Insurance (NHI) in 1995, there has been a database for health care in Taiwan. The NHI database includes health care data for more than 95% of the hospitals in Taiwan and more than 96% of the population receiving health care [8]. In 2006, the NHI covered most of the health care costs for 98% of the Taiwanese population.

This study was performed to evaluate the disease burden and epidemiological characteristics of varicella in Taiwan by using the NHI database to ascertain the age-specific incidences, geographic and seasonal distribution, hospital admission rate, complication rate, mortality rate, and medical costs related to varicella from 2000 to 2005 (from the introduction of private varicella vaccination to 1 year after public vaccination became available).

## Methods

### Data collection

Hospital inpatient and outpatient health care records for 2000 to 2005 were collected from the NHI database, and the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes related to varicella were analyzed for the population of Taiwan. The age-specific incidences, geographic and seasonal distribution, hospital admission rate, complication rate, mortality rate, and medical costs related to varicella were calculated. To calculate the annual population-based incidence, the annual incidence was calculated by dividing the number of varicella-related diseases by the population; population numbers for 2000 to 2005 were obtained from the Department of Statistics, Ministry of the Interior, Taiwan [9].

### Definitions

ICD-9-CM codes for varicella include the following: 052 chickenpox; 052.0 postvaricella encephalitis, postchickenpox encephalitis; 052.1 varicella (hemorrhagic) pneumonitis; 052.7 with other specified complications; 052.8 with unspecified complication; and 052.9 varicella without mention of complication.

Complications were defined as varicella with ICD-9-CM codes both for varicella (052 and the other related codes) and for varicella-related complications, which include the following:

- central nervous system, including 320 meningitis, 322 cerebellitis, 323 encephalitis, 348 encephalopathy, 351 facial palsy, 331.81 Reye's syndrome, and 780.3 febrile convulsion/seizure;
- skin and soft tissue, including 680 to 686 cellulitis and abscess, 035 erysipela, 728 pyomyositis and necrotizing fasciitis, 373 and 376.01 blepharitis, and 034 and 041 scarlet fever and streptococcal or staphylococcal infection;
- skeletal system, including 711 arthritis and 730 to 733 osteomyelitis;
- lower respiratory tract infection (LRTI), including 480 to 487 pneumonia, 510 to 519 pneumonitis, and 466 and 490 bronchitis;
- hematological system, including 287 thrombocytopenia, 283 and 285 anemia, and 288 neutropenia; and
- others, including 038, 790, 995.91 to 995.92 sepsis and bacteremia, 040-041 other bacterial infection, 422 cardiomyopathy, 425 myocarditis, and 070.5, 070.9, and 573 hepatitis.

Underlying diseases were defined as varicella with ICD-9-CM codes both for varicella (052 and the other related codes) and for varicella-associated underlying diseases, which include the following: 140 to 239 malignancy, 279 immunodeficiency, 260 to 269 malnutrition, V42 organ or tissue transplant, 580 to 589 nephrotic syndrome and nephrosis, 042 to 044 human immunodeficiency virus infection, 282 thalassemia, 691 atopic dermatitis, and 343.9 infantile cerebral palsy.

### Statistical analysis

For univariate analysis, categorical variables were compared with chi-squared or Fisher's exact test and continuous variables were analyzed by Student's *t* test. The difference in annual incidences among various age groups, the difference in annual incidences in different years, and the difference in seasonal distribution were measured with the appropriate chi-squared test. A $p$ value of $<0.05$ was considered to be statistically significant. All statistical analyses were performed with SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

## Results

### Age distribution and age-specific annual incidence

707,627 patients with varicella were enrolled in this population-based study from 2000 to 2005. The age distribution showed that 79.3% of all patients with varicella were children younger than 10 years. The peak age was 5 to 6 years, and preschool children accounted for approximately 66% of patients. Approximately 16% of patients with varicella were adults older than 20 years.

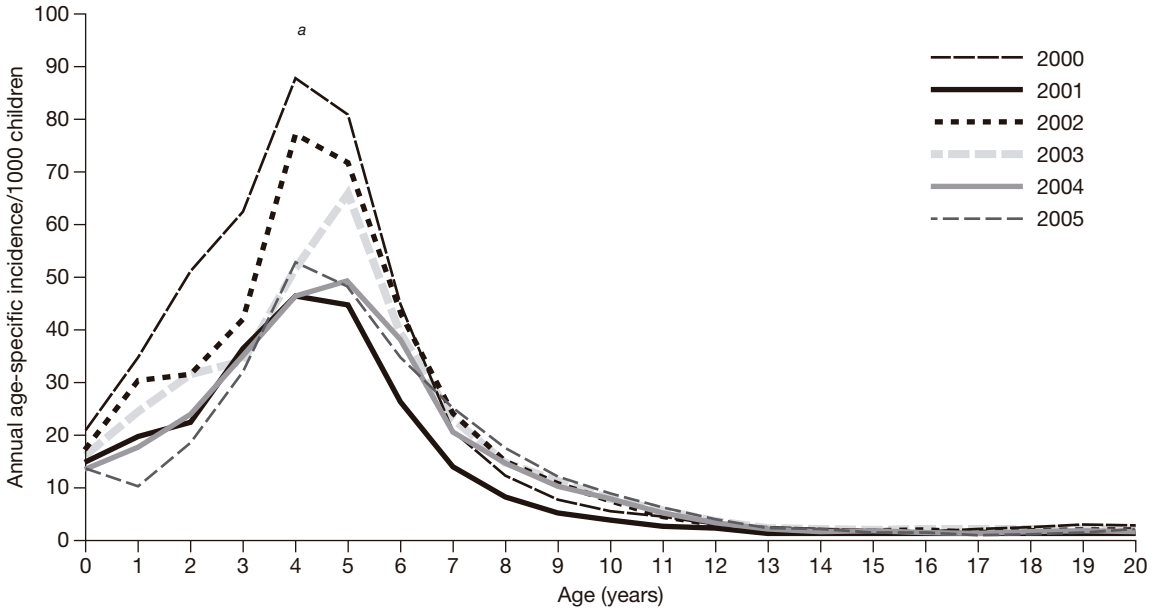


**Fig. 1.** Annual age-specific incidence of varicella infection from 2000 to 2005.
[a]$p < 0.001$ for 2000 (highest incidence) versus 2001 (lowest incidence).

Fig. 1 shows the age-specific annual incidence from 2000 to 2005. The age-specific incidence peaked at 4 and 5 years, regardless of the year, and the overall annual incidences were 60.5 and 60.2/1000 children for 4 and 5 years, respectively. The age-specific incidences of varicella beyond the first decade dropped to less than 10/1000 population (Fig. 1). The age-specific annual incidence among 4-year-old children was highest in 2000 (87.9/1000 population) and lowest in 2001 (46.6/1000) [$p < 0.001$]; the incidence remained constant from 2003 to 2005. A similar trend of age-specific annual incidence was also observed in other age groups of children younger than 10 years.

Sex did not affect the patient numbers or the over-all age-specific annual incidence (for 4-year-old children, the male incidence was 62.1/1000 population and the female incidence was 58.6/1000 population; $p = 0.85$).

## Geographic differences in annual incidence

As the highest annual incidences of varicella occurred in 3- to 6-year-old children, the annual incidences of this age group were analyzed among 6 different areas in Taiwan, including 3 areas with free public varicella vaccination (Taipei City, Taichung County, and Taichung City) and 3 areas without free public varicella vaccination until 2004 (Kaohsiung City, Yunlin County, and Taitung County). There was a significant geographic difference in annual incidence between the areas, with annual incidences being significantly lower in the 3 areas with free public vaccination than in the other 3 areas, regardless of year ($p < 0.001$). The incidence of varicella among 3- to 6-year-old children decreased markedly from 2000 to 2005 in the areas where free public varicella vaccination had been administered ($p < 0.001$).

The age-specific incidence of varicella for 3- to 6-year-old children in Taipei City decreased from 69.6/1000 population in 2000 to 33.0/1000 population in 2005 ($p < 0.001$). The declining trend was also seen in the other 2 areas; in Taichung City, the incidence for 3- to 6-year-old children decreased from 53.1/1000 population in 2000 to 20.8/1000 population in 2005 ($p < 0.001$), and in Taichung County, the incidence decreased from 80.7/1000 population in 2000 to 12.6/1000 population in 2005 ($p < 0.001$). This trend was not observed in the other 3 areas without free public varicella vaccination, in which the incidences fluctuated. Fig. 2 shows the geographic-specific annual incidences.

## Monthly distribution

Fig. 3 shows the seasonal distribution of varicella by month. The epidemic season for varicella was winter, particularly January, with cyclic epidemics occurring every 2 to 3 years.

## Complications

18,456 patients with varicella required hospital admission during the study period, of whom 7224 had

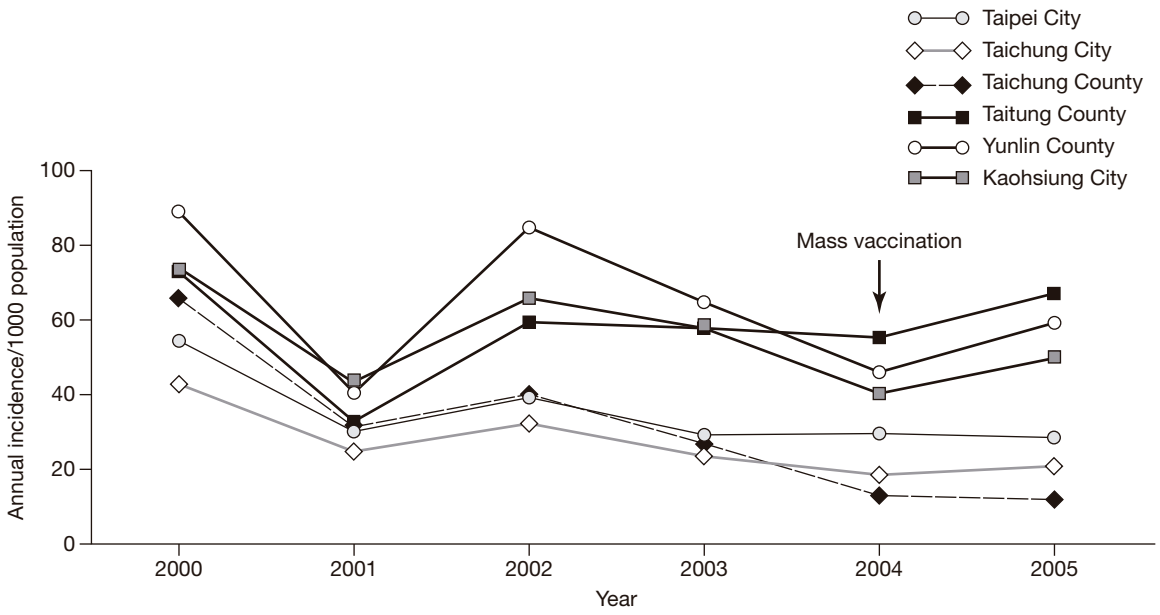


**Fig. 2.** Geographic-specific annual incidences of varicella infection among 3- to 6-year-old children from 2000 to 2005. [a]$p < 0.001$ for Taipei, Taichung City, and Taichung County compared with Taitung County, Yunlin County, and Kaosiung City.

complications. The overall varicella-related hospital admission rate was 60/1000 patients (95%CI, 48.5-71.5/1000 patients). Infants (46.2/1000 patients), 19- to 38-year-old adults (range, 41.7-72.8/1000 patients), and people older than 75 years (range, 47.5-166.1/1000 patients) had the highest hospital admission rates. The mean duration of hospital stay was 5.05 days (95%CI, 4.98-5.12 days).

The complication rate among patients admitted to hospital was 39.1%. LRTI was the most common complication (22.1% of patients admitted to hospital and 56.5% of varicella-related complications), followed by skin and soft tissue infection (12.5% of patients admitted to hospital and 31.9% of varicella-related complications) and other bacterial infection (3.5% of patients admitted to hospital and 9.0% of varicella-related complications) [Fig. 4]. Children had a higher complication rate than adults (46.8% for patients younger than 20 years vs 25.4% for patients 20 years or older, $p < 0.05$), and the peak complication rate was 54.9% among 1- to 5-year-old children. For patients younger than 20 years, the 3 most common complications were the same as those for all patients admitted to hospital, and the percentages were also similar. For patients older than 20 years, the most common complication was LRTI (13.4%), followed by hepatitis (6.5%) and skin and soft tissue infection (4.4%).

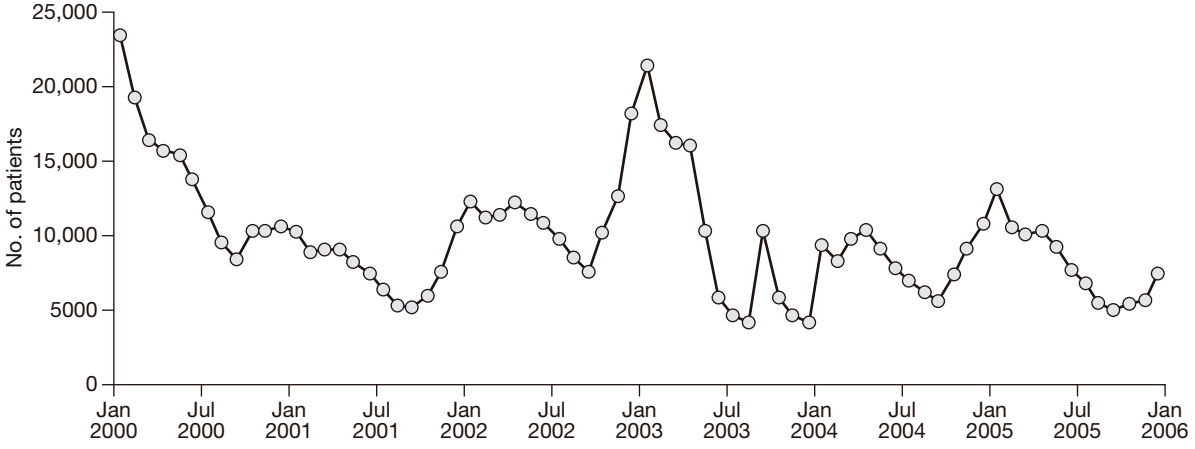


**Fig. 3.** Seasonal distribution of varicella infection.

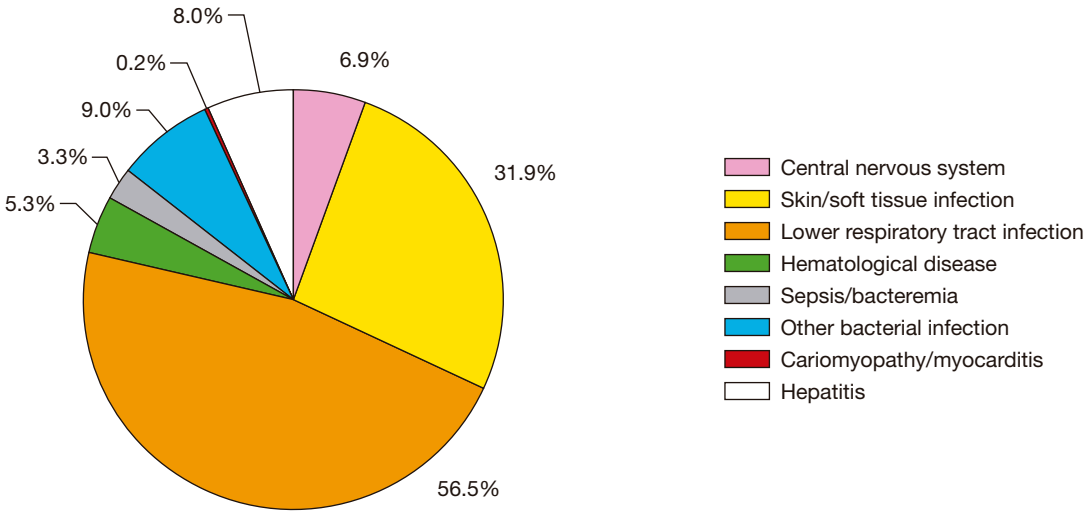


**Fig. 4.** Complications of varicella infection among patients admitted to hospital.

The incidence rate for complications among patients requiring intensive care was higher than that for patients admitted to hospital who did not require intensive care (58.8% vs 39.1%; $p < 0.0001$). The mean duration of hospital stay among patients with complications was 5.33 days compared with 4.88 days for those without complications ($p < 0.0001$); patients with complications also required a longer duration of intensive care than those without complications (mean, 6.30 days vs 4.36 days; $p < 0.0001$). Higher medical costs were incurred for patients with complications than for those without complications (mean NT$19,241/patient vs NT$13,451/patient; $p < 0.0001$).

## Underlying disease

Patients with underlying disease accounted for 3.3/1000 patients with varicella. Analysis of hospital admission and underlying disease revealed a higher proportion of underlying disease among patients admitted to hospital than among outpatients (4.17% vs 0.28%; $p < 0.001$). The age-specific rate of underlying diseases was relatively low for people younger than 40 years (range, 2.3-9.4/1000 patients), but this rate increased dramatically with age among people older than 40 years, reaching a peak of 42.3/1000 patients among those older than 80 years. The most common underlying disease was atopic dermatitis (56.6%), followed by malignancy (22%) and nephritic syndrome and nephrosis (9.1%). The 3 most common underlying diseases in children were the same as those for all patients with varicella, that is, atopic dermatitis (64.7%), malignancy (16.5%), and nephritic syndrome and nephrosis (6.9%), while the most common underlying diseases for all adult patients were malignancy (45.7%), atopic dermatitis (21.9%), and nephritic syndrome and nephrosis (18.6%).

From 2000 to 2005, 29 patients with varicella died. Table 1 shows the demographic characteristics of these patients. The median age of the patients who died was 16 years (range, 1-90 years); 14 patients (48%) were adults, 7 of whom were older than 60 years, and 15 (52%) were children, 13 of whom were younger than 5 years. Fifteen patients who died (52%) had underlying disease, 10 of whom had malignancy, and 21 (72%) had complications related to varicella, with the majority being septicemia and respiratory tract infection.

**Table 1.** Demographic characteristics of patients who died during hospital admission for varicella (n = 29).

| Characteristic | No. of patients (%) |
|---|---|
| Age (years; median) [range] | 16 (1-90) |
| Sex ratio (male/female) | 17/12 |
| Underlying disease[a] | |
| Malignancy | 15 (52) |
| Infantile cerebral palsy | 10 |
| Stroke | 1 |
| Diabetes mellitus | 1 |
| Chronic obstructive pulmonary disease | 1 |
| Metabolic disorder | 2 |
| Complication[a] | 21 (72) |
| Septicemia | 10 |
| Central venous system | 3 |
| Respiratory system | 10 |
| Cardiomyopathy | 1 |
| Skin and soft tissue | 2 |
| Unspecified | 4 |

[a]More than 1 per patient.

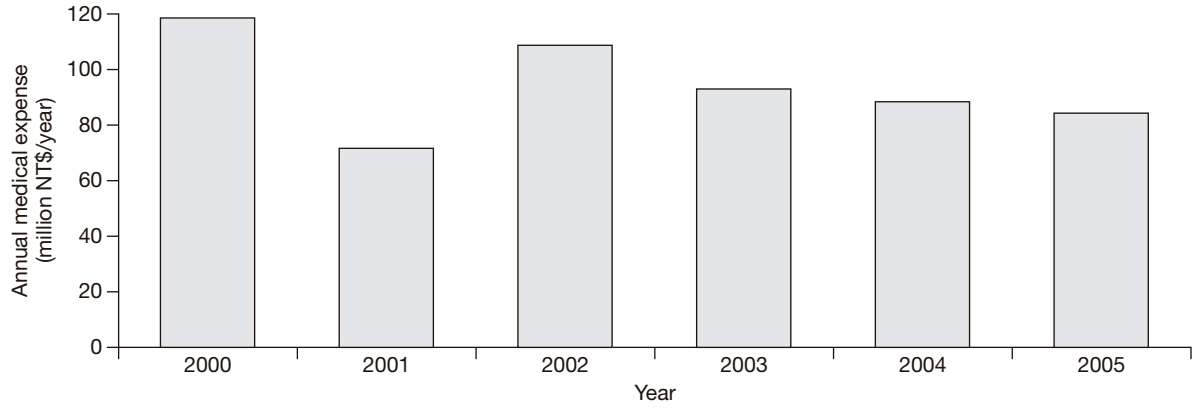


**Fig. 5.** Annual medical expenses for patients with varicella infection.

### Medical expenses

The annual varicella-related medical expenses were highest in 2000 (NT$118.6 million/year). In 2001, the medical costs decreased to NT$71.5 million/year, increased in 2002, and declined thereafter (Fig. 5). For medical expenses in the outpatient setting, the highest costs also occurred in 2000 (NT$82.1 million/year), with the trend following that for the total medical cost (range, NT$46.4 to 66.3 million/year). However, the annual costs for hospital admission fluctuated, with the highest costs in 2002 (NT$40.3 million/year) and the nadir in 2001 (NT$23.7 million/year). The total age-specific medical expenses peaked among children aged 0 to 10 years (NT$375.4 million/year); for the 4- and 5-year age groups, the age-specific medical expenses were 67.9 and 68.3 million NT$/year. The person-year cost was highest among elderly patients, particularly those older than 70 years (mean, NT$8478.9/person/year).

## Discussion

VZV poses a significant disease and economic burden worldwide. This study showed that most patients with varicella were younger than 10 years, indicating that varicella is primarily a disease of childhood, which is compatible with previous studies [10-13]. The incidence of varicella peaked in preschool age children in Taiwan and winter was the time of a seasonal peak in incidence. Seroepidemiological studies have shown that VZV-specific immunoglobulin G rapidly increases during the first decade of life and seropositivity reaches more than 90% [10].

The seasonal distribution of varicella shows a strong association with climate [14]. The incidence was higher in the cold weather in this study. This could explain why the nadir of annual incidence in almost all age groups occurred in 2001. According to the monthly weather data from the Central Weather Bureau in Taiwan, the highest mean temperature in January between 2000 and 2005 occurred in 2001. The incidence of varicella is not only associated with seasonal variations, but also varies among the different climate zones. VZV seroprevalence rates are lower in all age groups in tropical regions than in temperate climates [15-17]. Age-related incidence also varies and the mean age of patients with chickenpox is lower in temperate climates than in tropical climates [18]. Varicella has been shown to affect mainly adolescents and adults in tropical countries [17,19].

The varicella vaccine was first introduced as a private vaccination in Taiwan in 1997. Taipei was the first city to introduce free public varicella vaccination for children older than 1 year in 1998. Both Taichung City and Taichung County followed this vaccination policy in 1999. This program of mass vaccination was not applied in other parts of Taiwan until 2004. This study showed more than 50% decrease in the annual incidence of varicella in 3- to 6-year-old children in the areas with a free public vaccination policy, while the incidence in the areas with only private vaccination available fluctuated. Children who received vaccination between 1998 and 1999 in these 3 cities were aged 3 to 4 years in 2001, meaning that the impact of vaccination during the study period could be observed. Whether private vaccination given since 2004 has had an impact remains to be studied. A similar impact was observed in the United States, where the incidence of the disease was reduced by 85% after the implementation of universal immunization against varicella in 1995, with the largest decrease in incidence occurring in 1- to 4-year-old children [20].

Varicella usually occurs in childhood, and the medical expenses were highest for children younger than 10 years old, with a peak at the age of 4 to 5 years, in proportion to the number of patients with varicella. However, the hospital admission rates were much higher for the 3 age groups of infancy, adulthood (19 to 38 years), and elderly (older than 75 years). The highest hospital admission rate for elderly people was possibly due to their general health status. The hospital admission rates were associated with age-related person-year medical expenses, which were highest among elderly people, particularly patients older than 70 years.

The complication rate among patients admitted to hospital was 39.1%, which is lower than that observed in other studies of 53% to 100% [21-23]. The varicella-associated complications also vary in different regions and in different study populations. Infectious complications were the primary complications in several studies [22,24-27]. The results of this study showed that the most common complication was LRTI, either varicella pneumonitis or secondary bacterial infection, for both children and adults. LRTI accounted for more than half of the complications related to hospital admission. The age-specific complication rate among patients admitted to hospital showed that the highest complication rate occurred in the first decade of life, with a peak during the preschool age of 1 to 5 years; similar data have also been reported in Turkey [22].

Although varicella is acknowledged as a rare cause of death, there are few comprehensive reports of the clinical course leading to death, even in countries with universal varicella vaccination [28,29]. Of the 29 deaths in this study, children and adults accounted for a similar proportion. Some studies have shown that children, particularly infants, have a higher risk of death [30,31], whereas another study indicated that adult deaths due to varicella more than doubled in number, proportion, and rate per million population compared with that of children [32]. In this series, 15 of the 29 patients who died had underlying disease, with the majority being malignancy (n = 10). The immunocompromised condition was thought to be the predisposing factor for varicella-related death [30,31].

In conclusion, this study showed that most patients with varicella were younger than 10 years, and the incidence peaked among children aged 3 to 6 years. The incidence of varicella among 3- to 6-year-old children was significantly lower in areas with a free public vaccination policy. The hospital admission rates were higher in infancy and adulthood, particularly among elderly people, and the most common complication was LRTI.

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