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台灣地區2000至2004年腸病毒感染之生態及季節相關

Ecological and Seasonal Variations of Enteroviruses Infection in Taiwan, 2000-2004

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中文摘要

背景：

氣候變遷與全球暖化對於生態環境造成莫大的衝擊。極端的氣候型態以及每年溫度的逐漸上升，可能對具有溫度敏感性的病毒造成影響，如非小兒麻痺病毒型的腸病毒(non-polio enterovirus)，也更常發生於一年當中較高溫的季節。由腸病毒感染所引起的手足口病及疱疹性咽峽炎，主要好發於孩童身上，並在夏季及秋季伴隨著較高的發生率。過去在日本有研究指出，由腸病毒感染造成的手足口病及疱疹性咽峽炎，與氣溫及水氣壓之間存在著相關性。然而，目前針對腸病毒感染併發重症的生態及季節相關研究仍很有限。本研究將探討腸病毒併發重症個案、定點醫師通報手足口病與疱疹性咽峽炎之季節與生態相關。

方法：

利用行政院衛生署疾病管制局 2000 至 2004 年，腸病毒感染併發重症經病毒檢驗確認個案資料庫、定點醫師通報腸病毒感染個案資料庫，以及病毒實驗室檢驗資料庫，來分析腸病毒感染併發重症之人口學特性，並比較腸病毒重症患者與腸病毒感染患者在全台灣北中南東四個區域的分布情形以及其發生率的差異，進而連結氣象資訊，分析各季節及各月別腸病毒重症發生率、腸病毒感染通報率與季節、氣溫高低、降雨及日照之間的相關性。並利用多變相〔波以松迴歸, Poisson〕分析來估算相關潛在危險因子的相對危險性。

結果：

自 2000 年到 2004 年間，有 1573 個腸病毒感染併發重症的患者，其中 948 個案經確認，病例多好發於 5 歲以下孩童，佔率高達 94%。南部地區的重症發生率為每十萬人口 9.13，為最高，北部地區重症發生率則以每十萬人口 4.10 為最低。

季節性變化的分析部分則發現，一般而言六月是一年當中腸病毒重症發生的高峰期，但南部地區則是在十月份達到最高發生率。多變項分析結果顯示，男孩感染腸病毒重症的危險性比女孩高出了 43%，1 歲的小孩感染腸病毒重症的危險性最高，一歲孩子的相對危險性為 5 到 9 歲孩童的 28.9 倍〔95%信賴區間為 22.0~38.1〕。而南部地區孩童發生腸病毒重症的危險性比北部地區高出二倍；腸病毒重症的發生有隨氣溫上升而增加的傾向，和二月份別比較，其他月份均有高出的危險。定點醫師的通報則顯示，東部地區腸病毒感染之通報發生率最高，為北部地區約 3.5 倍；一年當中腸病毒感染通報的危險性以 5 月份為最高，而通報的危險性也有隨著溫度上升而顯著增加的趨勢。

結論：

台灣地區腸病毒感染有地區差異，其季節差異除與氣候有相關，也可能受到寒暑假的影響。由各地區每個月重症發生率的變化情形顯示，腸病毒的流行可能是由台灣其他地區傳播至南部地區，也可能和南部秋季較不同的氣象型態有關。

Abstract

Background:

The global warming and climate change have a great impact on the ecology. The temperature-sensitive viruses infection such as non-polio enteroviruses infection appears more frequently in higher temperature seasons. Hand, foot and mouth disease (HFMD) and herpangina are diseases of enteroviral infection occurring mainly in children with high incidence in summer and autumn. The epidemic of HFMD and herpangina has been associated with temperature and vapor pressure. However, studies on the ecological and weather variations of the severe enteroviral cases epidemic remain limited. The present study analyzed the ecological, seasonal and temperature variations associated with severe cases of the enteroviral infection and the HFMD and herpangina cases reported by sentinel physicians at local hospitals and clinics.

Methods:

We used data obtained from the Centers for Disease Control, Executive Yuan Department of Health to perform the study, including the surveillance data on severe cases of the enteroviral infection, database of HFMD and herpangina cases reported by sentinel physicians, and virology test results provided by virology laboratories. We measured the associations between demographic status and the severe cases, and the

HFMD and herpangina cases of enteroviral infection. We also investigated the geographic differences in the incidences of enteroviral infection cases with severe complication, and the reported rates of HFMD and herpangina in Taiwan. Seasonal and monthly incidence rates were measured and the associations with the weather status such as temperature, precipitation, and sunshine were analyzed. Multivariate Poisson regression analysis was used to calculate the relative risk of the enteroviral infection associated with the above potential risk.

Results:

Severe cases of enteroviral infection occurred mainly in children under 10 years of age, with 94% of cases occurred in children under 5 years of age. The highest incidence rate of enteroviral severe cases was in the southern Taiwan with the rate of $9.13/10^6$, more than two times greater than that for children in the northern area ($4.10/10^6$). Results showed an apparent seasonal variation. The epidemic peak of enteroviral severe cases occurred in June in most areas, but a second peak occurred in October in the southern area. The multivariate Poisson regression analysis showed that infants and children of 1-year-old had the highest risk for severe complicated enteroviral infection, with a relative risk (RR) of 28.9 (95% confidence interval (CI) 22.0-38.1) for 1-year-old children compared with children of 5-9 years old. This study also showed that the risk

of being severe cases was 43% grater for boys than for girls, 2.02 times grater (95%CI=1.72-2.37) for children in northern region than for children in the southern region. Cases of severe complication increased as the temperature increased, with the lowest rate in February and the highest rate in June. The rate of HFMD and herpangina cases reported by sentinel physicians was 3.5 times greater in the eastern region than in the northern region. In general, the HFMD and herpangina cases reported rates also increased as the temperature increased with the highest rate in May.

Conclusion:

There was a distinctive seasonal variation in enteroviral infection in Taiwan. The epidemic is associated with not only the weather but also school activities; the risk is decrease when children have no school in the winter and summer breaks. The monthly variations of the incidence by area show that the epidemic may spread from other areas to the south. The elevated incidence in the fall in the southern area is likely associated with the local weather.

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Chapter 1: Introduction

1.1 Background

General population have acknowledged the global warming associated climate change, with the concern of possible influence on the economy, public health, and the change of environment due to the climate change (Kellstedt et al. 2008). The emission of a large amount of greenhouse gases, including CO_2, CH_4, N_2O, CFCs and O_3 resulted from human activities, has been associated with global warming (Aitor et al. 2008).

The consequent impact of global warming has been of great concern in recent years. The global temperature increase may change the precipitation patterns, cause extreme weather events, and affect ecology of the world (Angell 1989). The United Nations Intergovernmental Panel on Climate Change (IPCC) has reported that the global temperature will increase for another 1℃ by 2020. Some of the amphibious animals will become extinction and more than 40 million population will lack of water (Houghton et al. 1996).

The extreme events such as tsunami, rainfall and drought due to the climate change may have already caused the epidemics of emerging infectious diseases, including malaria (Ye et al. 2007), dengue fever (Hales et al. 1996) and cholera (Patz et al. 1996) etc. In addition to these infection diseases, non-polio enteroviruses are also considered

as temperature-sensitive viruses, occurring more frequently in the summer, the higher temperature season during the year (Chen et al. 2007; Zhang et al. 2008). The epidemic of entrovirus 71(EV71) infection in 1998 summer and autumn in Taiwan was the highest in the Taiwan history (Ho et al. 1999). The study in Japan also founded that the weather condition parameters including temperature and vapor pressure are associated with the HFMD infection (Urashima et al. 2003).

The enterovirus infection usually causes acute and self-limited diseases characterized by sudden onset including HFMD and herpangina. A few patients may develop the severe disease or lead to death (Singh et al. 2002). The large outbreak of enterovirus infection in Taiwan in 1998 due to the EV71 caused thousands cases of HFMD in children. Besides the serotype of EV71, Coxsackievirus A16 (CAV16) was also the predominant enterovirus affected to human beings (Ho et al. 1999). Enterovirus infections are more prevalent in children under 5 years of age. And the incidence rates of enterovirus infection are different among the four regions of Taiwan (Chen et al. 2007).

1.2 Study Objective

Studies on the ecological and seasonal variations of enteroviruses infection and severe cases of infection in Taiwan were limited. This study used the Taiwan Centers for Disease Control surveillance data for severe cases of enteroviruses infection to observe the ecological and seasonal variations of the epidemic from 2000-2004. The research on HFMD associated with weather particularly with temperature, and vapor pressure in Japan has not emphasized the severe cases. The epidemic of severe cases of enterovirus infection in Taiwan has attracted great attention. The ecological and seasonal variations of the epidemic deserve further studies. This study used the surveillance data of HFMD and herpangina obtained from the Centers for Disease Control, Executive Yuan Department of Health to perform the study.

The specific aims of this study are:

(1) To investigate how the enterovirus infection is associated with the socio-demographic status.

(2) To investigate the geographic differences in the incidences of enterovirus infection in Taiwan.

(3)To investigate how the enterovirus infection is associated with the weather including season, temperature, precipitation, and sunshine.

Chapter 2: Literature review

2.1 The Types of Enterovirus

There are more than 60 serotypes of enterovirus. They are subgroups of single-stranded RNA belonging to the family of Picornaviradae (Zaoutis et al. 1998), including Coxsackievirus group A (types 1-22, 24), Coxsackievirus group B (types 1-6), three polioviruses, echoviruses (types 1-7, 9, 11-27 and 29-34) and enterovirus types 68-71(Ho 2000). The enteroviruses type 68 to type 71 are generally named as enterovirus type (Melnick et al. 1974).

2.1.1 The importance of non-polio enteroviruses

Because of the efficient vaccination program, polioviruses have nearly been eradicated. But the other non-polio enteroviruses remain as an essential cause of disease, due to the absence of vaccine and effective antiviral agents (Smith et al. 2004; Hsiung et al. 2000).

Chen et al. (2007) investigated enterovirus serotypes isolated from inpatients and outpatients with HFMD and herpangina from May 1998 to December 2005 in Taiwan. The serotypes found in the eight-year study including Coxsackievirus group A, Coxsackievirus group B, echovirus and EV71. Among these serotypes, EV 71 (23%) and Coxsackievirus A16 (CAV16) (23%) were the predominant serotypes. The rest

serotype identified were 13% of coxsackievirus B3 (CBV3), 6% of echovirus 4 (ECHO4), 5% of echovirus 6 (ECHO6) and 5% of coxsackievirus B4 (CBV4). These evidences also indicate that various types of enteroviruses have circulated in Taiwan (Chen et al. 2007).

2.1.2 The predominant enterovirus type in Taiwan

Among all types of the non-polio enteroviruses, EV71 is the most virulent to human beings, and CAV16 the second (Ho 2000). Since EV71 was the first time isolated in California in 1969, there have been at least 12 outbreaks associated with EV71 in the world. The EV71 infection has been considered as the most important type of enterovirus infection because of a high risk to cause severe cases or fatality (Ho et al. 1999).

Chen et al. (2007) have conducted a research to identify enterovirus serotypes for inpatients and outpatients with HFMD or herpangina diagnosed between May 1998 and December 2005. They found that the relative risk (RR) for EV71 infection was higher among inpatients than among outpatients (RR=16.02, 95% CI =13.38-19.19). In contrast, inpatients had lower risk than outpatients with CAV16 isolation (RR=0.58 and 95% CI 0.47-0.71) (Chen et al. 2007).

2.2 The infectious events of enteroviruses

2.2.1 The History of EV 71

(1) Early epidemic events

EV71 was first isolated in California in 1969 from the stool of an infant suffering from encephalitis (Schmidt et al. 1974). Since EV71 was identified in California, several epidemics have been reported. During the period from 1972 to 1977, there were 28 cases of EV71 infection identified in New York, some of whom were associated with severe neurological diseases, including aseptic meningitis, encephalitis and acute flaccid paralysis (Melnick 1984). There was an epidemic of aseptic meningitis in Melbourne in 1972-1973 in Australia, which was the first EV71 outbreak outside the USA (Kennett et al. 1974). EV71 infection was first linked to HFMD in epidemics in both Sweden (Blomberg et al. 1974) and Japan in 1973 (Gobara et al. 1977; Hagiwara et al. 1978). In 1978, another epidemic of EV71 in Japan caused a large number of HFMD cases with a high incidence of severe neurological complication disorders (Ishimaru et al. 1980).

(2) European epidemics, 1975-1978

In European countries, the first reported large outbreak and severe epidemic of aseptic meningitis and fatality due to the EV71 infection occurred in Bulgaria in May-September 1975, with 705 cases of febrile illness attributable to the virus. Among

them, 77.3% (545 cases) were identified as aseptic meningitis and 21.1% (149 cases) as acute flaccid paralysis. The majority of clinical cases occurred in children younger than 5 years of age and 83.8% of the paralytic cases were in this age group (Chumakov et al. 1979). In this Bulgarian epidemic, it is interesting to note that no cases of HFMD disease were reported in this epidemic event. EV71 was isolated from 25.3% of clinical diagnosed cases, and 100% of the fatal cases (Melnick et al. 1980).

The second large epidemic of EV71 infection occurred in European countries was in Hungary in May-September 1978. There were 323 cases confirmed as EV71 infection and 44 cases confirmed by peripheral samples. Among the severe neurological cases with EV71 infection confirmed, there were 13 cases of poliomyelitis-like paralysis, 145 cases of encephalitis and 161 cases of aseptic meningitis. Only four cases of HFMD were associated with EV71 infection (Nagy et al. 1982).

(3) Asia-Pacific Region epidemics

Several cases of HFMD were associated with the EV71 infection in Japan in 1973, which was also the first linkage between HFMD and EV71. Another epidemic in Japan occurred in 1978 and resulted in a large number of HFMD cases with the complications of aseptic meningitis, acute cerebellar ataxia and acute flaccid paralysis (Gobara et al. 1977; Hagiwara et al. 1978; Ishimaru et al. 1980).

An outbreak of EV71 infection reported in Hong Kong in 1985 also involved several cases identified as acute flaccid paralysis (Samuda et al. 1987). Before 1997, there was a circulation of EV71 causing several low-level endemics in Asia-Pacific area. The first EV71 epidemic record in China was in Hubei Province in the winter of 1987. This infection caused HFMD with no cases of acute flaccid paralysis or aseptic meningitis (Zheng et al. 1995). In the same year, another epidemic of EV71 infection associated with both HFMD and aseptic meningitis outbreaks was reported in Singapore (McMinn 2002).

Several epidemics of EV71 infection have been reported in the Asia-Pacific region since 1997. The first outbreak was occurred in 1997 in Sarawak, which caused 34 fatal cases (Cardosa et al. 1999). After this epidemic event, smaller outbreaks in Japan (Komatsu et al. 1999), peninsular Malaysia (Lum et al. 1998) and Singapore (Chang et al. 1998) were reported. These outbreaks have caused a great number of HFMD and herpangina among young children, including cases with neurological complications such as aseptic meningitis, cerebellar ataxia and acute flaccid paralysis (Chang et al. 1998; Lum et al. 1998). The outbreaks in Sarawak (Cardosa et al. 1999) and Malaysia were also caused some fatal cases (Lum et al. 1998).

The largest outbreak of EV71 infection reported to date occurred in 1998 in Taiwan,

which caused HFMD and herpangina in thousands of children with a high fatality. The epidemic occurred mainly in two waves, the first wave was in the period of March-July, and the second wave was in the period of September-November. The outbreaks caused 78 fatal cases, 71 of whom (91%) were five years of age or younger. EV 71 was present in 75% of hospitalized patients who survived, and 92% of patients who died (Lum et al. 2002).

High-level of EV 71 infection activity continually occurred in Asia-Pacific region during 2000-2001 in Sarawak, Singapore, Malaysia and Taiwan (Lum et al. 2002; Chen et al. 2007). In 2000, there were numerous cases of HFMD identified in Singapore and south peninsular Malaysia (Lum et al. 2002).

Studies on the Centers for Disease Control in Taiwan surveillance data have show that there were EV71 infections occurred annually between 1998 and 2005. The annual mortality rates varied significantly during the eight-year period (Chen et al. 2007).

2.2.2 The infectious due to other enteroviruses

(1) Coxsackie Group

Several studies have found Coxsackie group viruses the predominant types of enterovirus of HFMD in children. Among 237 patients identified in Shenzhen, 133 (56.1%) were RT-nPCR positive, including 48.1% positive for CAV16, 28.6% for EV71

and negative for rest of 23.3% (Zhang et al. 2008).

Another study, on the HFMD epidemic with 72 cases in children occurring in April-June 2002 in Shanghai, found a total positive rate of 81% for CAV16 (58 of 72) and 12.5% for EV71 (9 of 72), with the CAV16 to EV71 ratio of 6.4:1 (Yang et al. 2005). The Coxsackie viruses caused HFMD are mostly related to the CAV16 infection. Some other enteroviruses also have been associated with HFMD epidemics, such as CAV4, CAV5, CAV9, CAV10 and EV71 infections (JL 1996).

Niigata Prefecture is a prefecture located on Honshū island on the coast of the Sea of Japan. A study was carried out in this Prefecture in 2001 to investigate the seral types of enterovirus for HFMD patients. Among the patients, 76.3% (29 of 38) of petients were infected by CAV16, 5.3% (2 of 38) infected by CAV5, 2.63% (1 of 38) infected by Coxsackievirus B4 (CBV4) and 2.63% (1 of 38) infected by ECHO4 (Watanabe et al. 2002).

(2) Echoviruses

In July-September of the year 2003 in Shangdong Province of China, a large scale of HFMD outbreak affected more than 150 children with obvious symptoms. Nearly half of the patients had herpangina or severe symptoms including aseptic meningitis, encephalitis, and myocarditis. Besides EV71 and Echovirus30 (ECHO30), Echovirus 19

(ECHO19) infections associated with HFMD were also identified (Zhu et al. 2007).

There was an endemic of HFMD reported in Malaysia in 2000, with over one hundred cases of mild HFMD. Among 111 enteroviruses isolated, there were 68.5% (76/111) of EV71, 18.0% (20/111) of CAV16, 1.8% (2/111) of Coxsackievirus B, and 11.7% (13/111) of ECHO7. However, the fatal cases of viral encephalitis were associated with the ECHO7 infection (Lum, et al. 2002). This outcome was different from the finding in the previous study in India (Madhavan et al. 1969).

2.3 Characteristic of Enterovirus Infection

2.3.1 Symptoms

The clinical manifestations of enteroviral infection are protean in nature. More than 50% of enterovirus infected persons have no symptom or very mild symptoms including diarrhea, febrile and red rashes. A part of infected persons may develop specific type of disease like HFMD or herpangina, and usually without ife-threatening manifestation. A small proportion of cases may be complicated by severe disease including aseptic meningitis, encephalitis, myocarditis, pericarditis, pneumonitis and paralysis. Patients of HFMD or herpangina being complicated by severe diseases are more dangerous and may sometimes lead to death. (Enterovirus_Centers of Disease Control, R.O.C, 2008)

2.3.2 Clinical Definitions

(1) HFMD and Herpangina

Patients who have vesicular lesions on their hands, feet, mouth, and buttocks are defined as HFMD. Another unique disorder of enteroviruses infection is herpangina. Patients with herpangina always have symptoms of vesicular exanthema on the fauces or soft palate; besides, it is sometimes accompanied by febrile, fever, sore throat, and pain on swallowing. Fortunately, most patients with these manifestations alone are seen as outpatients (Chen et al. 2007).

(2)Severe Cases

Patients hospitalized with HFMD or herpangina may also have other symptoms or signs of serious illness. Patients of HFMD or herpangina with a complication, such as aseptic meningitis, encephalitis, or acute flaccid paralysis; pulmonary hemorrhage or pulmonary edema; or myocarditis, are defined as severe complicated enteroviral infection cases (Ho et al. 1999). The symptoms of aseptic meningitis include headache, meningeal signs, and mononuclear pleocytosis (over 5 x 10^6 leukocytes per liter if the patient was older than 1 month, or over 25 x 10^6 leukocytes per liter if the patient is a newborn) with a negative bacterial culture. Encephalitis has a feature with a disturbance in the level of consciousness, such as a lethargic sleep or coma (Ho et al. 1999; Chen et al. 2007).

Pulmonary edema is characterized by respiratory distress, tachypnea, tachycardia, frothy sputum, and rapidly progressing, patchy, diffuse pulmonary infiltrates and congestion on a chest film. Pulmonary hemorrhage is defined as bleeding during tracheal exhalation. Cardiopulmonary collapse is defined as the development of hypoxemia and low blood pressure, regardless of the administration of inotropic drugs (Ho et al. 1999; Chen et al. 2007).

The patient who has acute onset of paresis or paralysis of one or more

skeletal-muscle groups, usually of one or more limbs, are defined as acute flaccid paralysis. Myocarditis is characterized by the evidence of diminished contractility on echocardiography, arrhythmia, an enlarged heart, and elevations in cardiac enzymes that are the indicators of cardiac damage (Ho et al. 1999; Chen et al. 2007).

2.3.3 Sero-epidemiological Studies in Taiwan

The enteroviral infection outbreak occurred in 1998 in Taiwan has attracted great attention. Investigators investigated the sero-epidemiology of EV71 after the outbreak. Serums collected by Chang et al. (2002) before and after the 1998 EV71 epidemic were compared. They randomly selected 539 serum samples that had previously stored at Chang Gung Children's Hospital and Chang Gung Memorial Hospital as pre-epidemic specimens. Those 539 serum samples were collected from those healthy children who received health examinations or participated in vaccine trial. In the meanwhile, they also collected specimens from adults who received health examinations between July and December 1997. After the outbreaks of EV71 had ended, the study team collected serum samples from 4619 individuals residing in Taoyuan, Ilan, Taichung, and Kaohsiung counties, Taipei city, and Kaohsiung city in January- July 1999 (Chang et al. 2002).

The Chang Gung study showed that more than half of adults in Taiwan have EV71 antibody and were possibly immune to EV71 before the epidemic. The sero-positive

rates in children in 3 to 12 years of ages were ranging from 26% to 50%. Children of 3 years of age and younger had the lowest antibody levels from 4% to 26%. (Ho 2000) The serum comparison showed that children under 3 years of age with the lowest sero-positive rates in July - December 1997 were the majority (69% [102 of 147]) of severe and fatal (86% [24 of 28]) cases during the EV71 epidemic (Chang et al. 2002). This study proves that children with low sero-prevalence rates of EV71 in the pre-epidemic period had elevated mortality rates and severe case rates during the epidemic. Age-specific EV71 sero-positive rates before the epidemic were significantly negative to age-specific mortality rate throughout the epidemic.

Lu et al. investigated the sero-epidemiology of EV 71 in 81 children born in the year of 1988 with yearly blood samples taken from 1988 to 1998. The incidence of EV 71 sero-conversion increased yearly among these children in 1989-1997, ranged from 3% to 11%. By the year of 1997, approximately 68% children were identified as EV 71 infection (Lu et al. 2002).

2.3.4 Age-specific and gender-specific enterovirus Infection

During the first outbreak of enteroviruses infection in Taiwan in 1998, there were 129,106 reported cases of enteroviral infection from March 29 through the end of the year. There were 405 severe cases among all patients, most of them were 5 years old or

younger (Hsiung et al. 2000). About 80% (314 of 393) of the hospitalized patients were younger than five years old, and the children less than one year of age were most likely to be hospitalized. Among 78 fatal cases, over 90% (71 of 78) were children of five years of age or younger, fatality rate was remarkably higher among the children aged below one year old, compared to those who were older (Ho et al. 1999).

There were a total of 1548 severe cases of HFMD or herpangina reported to the Taiwan CDC from 1998 to 2005 (Chen et al. 2007). A great portion (92%) of patients were children younger than 4 years of age, and with 74% occurred in children younger than 2 years old. This study also found the case fatality rate was significantly higher in children younger than one year old.

Chang et al. (2002) investigated the risk factors associated with EV 71 infection in preschool children, but found no significant difference between boys and girls in the EV71 infection. Chen et al. (2007) analyzed the 1,548 severe cases of HFMD or herpangina reported in 1998-2005 to investigate the sex difference on the fatal outcome of HFMD/herpangina severe cases. They did not find that the mortality rate of EV 71 infection was significantly different between boys and girls. There studies demonstrate that enterovirus infection in the young children disease with no difference between boys and girls.

2.4 Ecology patterns of enteroviral infection in Taiwan

2.4.1 Geographic Distribution

The outbreak of EV71 infection in 1998 in Taiwan caused thousands cases of HFMD and herpangina, some of whom died in that epidemic. There were 405 patients with severe complication in all regions of the island, most of whom were under five years of age, the susceptible group. In order to finding regional difference in the enterovirus epidemic, Ho et al. (1999) separated the island into four regions including northern, central, southern and eastern region. The northern region, including Taipei, had more severe cases than other regions in the epidemic. The incidence rates of severe cases were not significantly different among the four regions, but the case fatality rates were significantly different among the four regions. The central region including Changhua had the highest case fatality rate and the eastern region had the lowest case fatality rate.

Another ecological research also separated the island into four regions to investigate the geographical difference of enterovirus morbidity from 1998 to 2005 (Chen et al. 2007). Their findings were approximately similar to the findings reported by Ho et al. (1999), the central region had the highest incidence and the eastern region had the lowest incidence. The case fatality rates were different among the four regions.

2.4.2 Urban and Rural Area

For the nationwide outbreaks of EV71 infection in 1998 in Taiwan, Chang et al. (2007) also investigated the urban and rural difference of EV71 morbidity. In this study, areas with a population density of 1500 or more people per square kilometer were defined as urban areas, otherwise, areas with a population density less than 1500 people per square kilometer were defined as rural areas. In addition to the metropolitan areas of Taipei and Kaohsiung cities, Taoyuan, Taichung, Kaohsiung, Ilan counties were also included in the study areas representing northern, western, southern and eastern Taiwan, respectively. Serum samples were also collected from 4619 persons in those six areas. The mortality rates were analyzed, children younger than 3 years of age had the highest mortality rate. Among all the study areas, Taoyuan County had the highest mortality rate. The metropolitans, Taipei and Kaohsiung had the lowest mortality rates. With the highest population densities, the post-epidemic sero-prevalence rates of EV71 for the high-risk age groups were significantly lower in the two metropolitan areas than in the other four counties. These sero-prevalence rates were also associated with the mortality rates among different age groups in every area. This study also found that living in a rural area was at a higher risk correlated to EV71 infection in preschool–aged children. This is because larger family members in rural families increase the odds of infection

(Chang et al. 2002). Although, Ho et al. (2000) indicated that this type of relation was still unclear.

2.5 Enteroviral infection and Climate

2.5.1 Seasonal Variation of Enterovirus infection

Enteroviruses infection has become a worldwide public health problem. In tropical and subtropical area, the enterovirus infection with high incidence can be found throughout the year with minor seasonal variation. In contrast, the infection in the temperate climate area is more commonly detectable in summer and autumn than in winter and spring (Strikas et al. 1986). Enteroviruses are thus referred as “summer viruses” with the infection primarily occurs in the warmer months, especially from May to October in the United States (Zaoutis et al. 1998).

The strong seasonality of HFMD and herpangina suggests that the disease prevalence attribute to climate contribution (Abad et al. 1994). This characteristic explains that enteroviruses infection often occurs in summer and autumn in Taiwan, similar to the other temperate regions (Ho et al. 1999; Chen et al. 2007).

Previous studies found that the number of HFMD and herpangina cases increased remarkably from the week of March 29, 1998, through the week of December 27, 1998, in the notable outbreaks of enterovirus in Taiwan (Ho et al. 1999). Cases reported to the Centers of Disease Control, Taiwan (CDC, Taiwan) demonstrated the peak incidence in the early June. The number of HFMD cases reached a peak about the same time with

another small peak in October due to increased cases in southern Taiwan (Ho et al. 1999).

From March 1998 through December 2005, there were about 1,548 cases of HFMD and herpangina accompanied with severe complication reported to CDC in Taiwan. During the eight-year period of research, the epidemic peaks could be found in all years, mainly in the summer seasons (Chen et al. 2007).

Furthermore, the epidemic may reach a peak at difference week interval in the year among areas. The epidemic peak appears one week earlier in central Taiwan, while the peak appears in the southern area one and a half weeks late. There are two waves of the epidemic during the whole year, one in summer and the other in autumn. The first wave (summer) of the epidemic is generally spreaded island-wide in Taiwan. Nevertheless, the second wave (autumn) has a peak generally limited to southern region. This wave starts from September lasts to the second week of December with a small peak appears in the first week of October (Chen et al. 2007).

The seasonal pattern of HFMD infection in Shenzhen does not have a fall wave. Among 237 diagnosed cases in 2001-2004 years, there were more cases in springs and summers (Zhang et al. 2008).

2.5.2 Enterovirus Infection Related to Weather Parameters

Taiwan is located between 21°53'50"and 25°18'20" north latitude and lies in a moderate subtropical climate area. It has a seasonal pattern of enteroviruses infection, as above mentioned, more prevalent in summer and autumn. The epidemic waves in Taiwan are similar to other temperate regions in the world (Chen et al. 2007). This seasonal pattern may actually reflect the climate conditions such as temperature, pressure, precipitation and sunshine level.

Urashima et al. (2003) have established a seasonal model to simulate the annual fluctuation of herpangina and HFMD associated with the weather condition in Tokyo. The researchers obtained data for 54 weather condition parameters from the Meteorological Agency and data of HFMD and herpangina patients from the Infectious Agents Surveillance Report in 1987 to 2002. They found a significant simple association between the number of HFMD and herpangina cases and the air temperature and vapor pressure. When the average temperature is higher than 19℃, the cases of HFMD and herpangina increase apparently. Besides, when the vapor pressure excees to a threshold of 15 hPa, the cases also sharply increases (Urashima et al. 2003).

The enteroviruses infection associated with weather conditions has not been well investigated. This thesis study aims to investigate mainly the association between the infection and weather status among regions in Taiwan.

Chapter 3: Materials & Methods

This study aims to investigate the ecological variation of enterovirus infection and the association with weather in Taiwan. The results were presented in three parts.

For the first part, we analyzed the epidemiological patterns of enterovirus severe cases, including the distributions of cases by age, gender, and regions in Taiwan. Besides, we also observed the seasonal variation of enteroviral severe cases, and to analyze the association with temperature, rainfall and sunshine.

For the second part, we used the surveillance data on HFMD and herpangina cases reported by sentinel physicians, obtained from the Centers for Disease Control, Executive Yuan Department of Health, to compare the relationship between reported cases and weather condition (temperature, rainfall hours and sunshine hours) among regions in Taiwan.

In the third part, we used the database from Virology Contract Laboratories to analyze the association between weather condition and the positive rate for the tests of enterovirus severe cases.

3.1 Study area

For the ecological comparison, the cities and counties in each region were shown as following:

(1). Northern region: Taipei City, Taipei County, Keelung County, Ilan County, Taoyun County, Hsinchu City, Hsinchu County.

(2). Central region: Miaoli County, Taichung City, Taichung County, Changhua County, Nantou County.

(3). Southern region: Yunlin County, Chiayi City, Chiayi County, Tainan City, Tainan County, Kaohsiung City, Kaohsiung County, Pintung County.

(4). Eastern region: Hualien County, Taitung County.

3.2 Definition of terms

(1). Age: ages were stratified as: <1, 1-2, 2-3, 3-4, 4-5 and 5-9 years

(2). Season:

Spring: March, April, May

Summer: June, July, August

Autumn: September, October, November

Winter: December, January, February

(3). Sentinel physicians: There were about 650-800 sentinel physicians selected by the Public Health Bureau covered 70-80% of area in each county. They were representative doctors in their counties to involve in the case report system.

(4). Virology Contract Laboratory: There were 13 virology contract laboratories in

Taiwan. These laboratories collected samples base on the CDC surveillance system for monitoring enterovirus and influenza infection.

3.3 Study materials and data sources

(1). Centers of Disease Control: database of enteroviruses severe cases (2000-2004) and the database of Virology Contract Laboratory (2000-2004) and database of sentinel physician reported (2000-2004).

(2). Central Weather Bureau: Weather database (2000-2004).

(3). Department of Statistics, Ministry of Interior: Population information.

3.4 Statistical Methods

(1). Part I. We used the database obtained from CDC to analyze the characteristics of enteroviruses severe cases. In order to compute the incidence rate of enterovirus severe cases, we obtained the population data. Incidence rates by age and sex, region were estimated and the risk of the severe cases associated with these variables were calculated using Poisson regression analysis. Data analysis also estimated the rates and risks associated with season and weather status.

(2). Part II. Data analysis on the epidemic patterns of sentinel physicians reported data emphasized the number of HFMD and herpangina cases and the rate by region. The annual epidemic curve was calculated. Poisson regression analysis

were also used to calculated the RR associated with year, region and weather parameters.

(3). Part III. The rates of positive enteroviral test results among samples reported by the virology contract laboratories were calculated. Whether the positive rate associated with weather parameters was also observed.

Chapter 4: Results

4.1 Enterovirus severe cases

4.1.1 The distribution of enteroviral severe cases by age and gender

In 2000-2004, 60.3% (948/1573) of reported enteroviral severe cases were serologically confirmed for children less than 10 years of age (Table 1). Among these confirmed severe cases, over 94% (887/948) were less than 5 years of age, and more than half were children in 2 years of age or younger (Table 2). The incidence was the highest in 1-year old children and decreased to the lowest rate in children in 5-9 years of age. The incidence rate was consistently higher for boys than fro girls in each age group (Table 2).

4.1.2 The distribution of enteroviral severe cases by region

The age-specific distributions of severe cases among the four regions were somewhat similar (Table 3 and 4). With 60.3%% confirmed cases, incidence rate was the highest in the southern region (9.13 per 100,000), followed by the central region, the eastern region, and the lowest in the northern region (4.10 per 100,000). Among all age-specific rates by region, children in 1-year of age in the southern region had the highest incidence of 31.3 per 100,000 (Table 4).

The chronological analysis showed that the epidemic of enteroviral severe disease

peaked in 2001 for both number of cases (Figure 1-1) and incidence (Figure 1-2). The incidence dropped dramatically to the lowest in 2004. The overall chronological incidence rates were 12.7/per 100,000 in 2001 and 1.8/per 100,000 in 2004. The incidence was highest in the southern region in 2001 (18.0 per 100,000) and the eastern region the second. No cases were confirmed in the eastern region in 2003 and 2004 (Figure 1-2).

4.1.3 The distribution of severe cases by month

The analysis of annual incidence of severe cases by month showed that the epidemic occurred by two waves during the year. The first wave had a peak in June, and the peak in the second wave occurred in October (Figure 2-1 and 2-2). The average incidence in 5 years increased from 1.01 per 1,000,000 in February to 9.4 per 1,000,000 in June with a second peak of 7.68 per 1,000,000 in October. The monthly incidence by year shows that the highest incidence was 22.3 per 1,000,000 in June in 2001 (Figure 3-1 and 3-2). The epidemic patterns of monthly incidence by region showed that the epidemic in the southern region was different from that of other regions. Although, all regions had the first peak in June, the epidemic curve for the southern region had a second peak with the highest incidence of 14.8 per 1,000,000 (Figure 2-2).

4.1.4 Univariate analysis

Data analysis also estimated relative difference in incidence by sex, age and region. The results of univariate showed that boys were 44% more likely than girls to have the diseases (Table 5). The risk of enteroviral severe cases infection was the highest in children of 1≦ years of age compared with the children in 5-9 years of age. The incidence rates in the southern and central regions were significantly higher than that in the northern region with a southern region to northern region relative risk of 2.23 (95% CI=1.91-2.60).

Incidence rate ratios were also calculated between epidemic years, seasons and months. Compared with the incidence of 2004, the rate ratio was the highest in 2001 (RR=7.11, 95% CI=5.30-9.54) (Table 6). The seasonal comparison showed that the risk of having the enteroviral severe cases was the highest in summer with a rate ratio of 3.06, followed by autumn and spring, compared with winter. The highest risk month of enteroviral severe cases infection occurred in June with a rate ratio of 5.58 (95% CI=3.28-9.51), followed by May, compared with the lowest rate of February (Table 6).

In order to verify the seasonality of the disease, relative risk associated with the weather parameters such as temperature, rainfall and sunshine were also analyzed. The results showed that the daily average temperature was probably a better indicator then the daily maximum temperature or the daily minimum temperature in the risk

estimation (Table 7). The risk increased as the daily average temperature increased till 29.9℃. The lower hours of average daily rainfall had no consistent association with the significantly difference. The risk of enteroviral severe cases was also related to the hours of average daily sunshine significantly (Table 7). Using average daily sunshine of 2.50-4.99 hours as reference, the risk increased as the sunshine hours increased with a dose-response. There was also an increased risk when there was no much sunshine.

4.1.5 Multivariate analysis

We used the multivariate Poisson regression analysis to adjust the risk measures for enterovirus severe cases associated with age, gender, region, and daily average daily temperature and hours of sunshine. The results showed that the risk of being infected remained 43% greater for boys than for girls (Table 8). Children of 1-year old remained at a higher risk (RR=28.9, 95%CI=22.0-38.1), compared with children in 5-9 years of age. Regional differences changed slightly in the four regions. The monthly differences remained; the risk increased starting from February, reached a value of 5.50 (95%CI=3.00-10.1) peak in June, declined in July and September. The relative risk reached another peak of 5.14 (95%CI=2.84-9.29) in October. The temperature was not a significant factor associated with the diseases.

To avoid the over-adjustment, we excluded month and calculate the relative risks

for factors associated with enteroviral severe cases. The results showed that the risk of enteoviral severe cases increased as temperature increased, compared to temperature lower than 15℃. The length of daily average sunshine was not a significant factor associated with the risk of enteroviral severe cases (Table 9).

4.2 Sentinel physicians reported data

4.2.1 Physician reported cases by region

There were 531865 of enteroviral infection cases reported by sentinel physicians in 2000-2004 (Table 10) with the largest number of cases in 2000. The lowest reported rate for HFMD and herpangina cases was 2.68 per 10^3 in Northern region and the highest rate was 9.41 per 10^3 in the eastern region (Table 11).

4.2.2 Case reported by sentinel physician at hospital

Weekly cases of HFMD and herpangina reported by sentinel physicians affiliated with hospitals were analyzed. In 2000-2004, we noticed for each year that the average cases reported by each sentinel physician were higher in the weeks of 16^{th}-25^{th}, ranged from 8 to 11 cases (Figure 4). However, there was another peak appeared in the 40^{th}-48^{th} weeks in 2004. This autumn peak was mainly contributed by the herpangina cases (Figure 5-1). The sentinel physicians reported more cases of herpangina (Figure 5-1 and 5-2). Physicians in the southern region reported more cases of HFMD and herpangina weekly than physicians in other region did (Figure 6-1~6-5).

4.2.3 Cases reported by sentinel physicians at clinics

Figure 7-9s show the weekly cases of HFMD and herpangina reported by sentinel physicians at clinics. The cases increased in the 13^{th} -15^{th} weeks (March) and reached to

a peak in the 19th - 27th weeks, or in May and June (Figure 7). In the year of 2004, there were also two epidemic peaks, but with less average cases reported by the physicians at clinics than by the physicians at hospitals. The second peak was also contributed by herpangina (Figure 8-1). More herpangina cases than HFMD cases were reported by sentinel physician at clinics (Figure 8-2). Figures 9-1~9-5 shows the patterns reported among four regions.

4.2.4 Risk factors associated with physicians reported cases

The multivariate Poisson regression analysis showed that the disease was 3.51 times more likely to be reported in the eastern region than in the northern region. The relative risk was the highest in 2000. Monthly comparison showed that the highest risk for reporting HFMD and herpangina was in May, followed by June (Table 12).

The multivariate Poisson regression model was also used to analyze whether the reported rate of HFMD and herpangina was associated with weather parameters. Compared with the temperature < 15℃, the RR increased from 1.67 with the weekly maximum temperature of 15-19.9℃, to 6.39 with the temperature of ≧30℃. The disease had a significant revealed association with the rainfall, but no association with the average weekly sunshine hours (Table 13).

Chapter 5: Discussion

5.1 The age variation of enteroviral infection

HFMD and herpangina are the typical common contagious illness of infants and children caused by virus belonging to the enterovirus genus. In General, minor symptoms appear from the infection and produce antibody to counteract the disease after the infection. Except being infected by other group of enterovirus, children may not have a second infection. Only few patients of HFMD/herpangina may have complications. The present study found that among sentinel physicians reported 531,865 HFMD/herpangina cases in the year of 2000-2004, there were 948 enteroviral severe cases, equivalent to a rate of 1.78 per 1000 mainly in children under 5 years of age.

In an outbreak of EV71 infection in Bulgaria in 1975, 83.8% of severe cases woccurred in children younger than 5 years of age (Chumakov et al. 1979). Another study in Japan found that 12 of EV71 infection severe cases were children younger than 10 years of age, with 75% (9/12) cases in children younger than 5 years of age, or 33.3% cases less than 1 year of age (Komatsu et al. 1999). Our study shows that the pattern of age distribution is similar to their studies. The enteroviral infection occurred mainly in children younger than 5 years of age with the highest risk for 1-year old children, followed by children younger than 1 year of age. The incidence in fact varies

among regions in Taiwan. Zaoutis et al. (1998) indicated that the infections occurred mainly in children lack of immunity and with poor healthy habits (Zaoutis et al. 1998). It is not clear whether the incidence variation among regions in Taiwan is associated with differences in immunity and health behavior.

In the present study, we did found that the incidence of HFMD and herpangina based on sentinel physicians' reports was the highest in Eastern Taiwan and the lowest in the Northern Taiwan. But the risk of severe cases was the highest in Southern region and the lowest in Northern region. Children in ages of 1 year and less were at the highest risk. But the differences in incidence rates and between infants and children of 1 year of age varied among regions.

Further analysis on the incidence by region and chronological year showed that the incidence rates in both 2000 and 2001 were the highest in the Southern region and followed by the Eastern region and Central region. The incidence rate in Southern region and decreased to a level lower than that in Central region in 2003 and 2004. There was no case reported for the Eastern region in 2003 and 2004. High incidence rate in earlier years in the Southern and Eastern regions might have established herd immunity for children to avoid the epidemic in 2003 and 2004.

5.2 The gender difference

The present study showed that a risk of being severe cases was 39% grater for boys than for girls. Chen et al. (2007) also found previously in Taiwan that boys are at higher risk of severe cases infection, but there is no significant difference in the fatality between boys and girls. Poor hygienic behavior and high activities may have association with the higher infection rate for boys. But it remains unclear why the risk of enteroviral severe infection is grater for boys.

5.3 The trends of enteroviral infection by chronological year, season and month

The enteroviral infection severe cases declined annually after the large scale outbreak in 1998. Another epidemic elevation occurred every 2 to 4 years due to the accumulation of susceptible population. From the outbreaks of enterovirus infection in 1998, the severe cases immensely decreased in 1999, against 291 cases in 2000 and reach a peak of 391 cases in 2001. The severe cases decreased sharply in 2000-2004. (Figure 1, Appendix 6).

This study found that the risk of enterovirus infection was the lowest in winter, and the highest in summer, followed by autumn. Zaoutis et al. (1998) suggested that enteroviral infection mainly occurred in the temperated seasons such as May-October in the temperated north hemisphere. However, enteroviral severe cases decreased in July-August, the seasons with the highest temperature. Chang et al. (2007) considered

that this is because of limited person to person contacts while children are more likely confined to home during the summer break of the school. Our study did show that there were least cases in February is the cold month during the year and the schools are in winter break. Less person to person contacts may curb the spread of the virus.

5.4 The regional difference

Ho et al. (1999) found the lowest incidence rate in the 1998 outbreak occurred in the eastern region, but no significantly different from other regions. Chen et al. (2007) also reported that the incidence of enteroviral severe cases occurred in 1998-2005 was the lowest in the eastern region.

We found that the incidence rates of enteroviral severe cases in 2000-2004 was the highest in the southern region ($9.13/10^6$) and the lowest in the northern region ($4.10/10^6$) among four regions. The physician reported incidence of HFMD/herpangina was also the lowest in the northern region, but the highest in the eastern region (Table 11). In fact, the severe cases to HFMD/herpangina cases ratio was the highest in the northern region but the lowest in the eastern region. The regional variations in the incidences of severe cases, HFMD/herpangina and the severe cases to HFMD/herpangina ratios may have relationship with the population density, population hygiene and herd immunity. The sentinel physicians reporting behavior may affect the surveillance completeness as well.

We have observed a two mode of cases in the seasonal epidemic curve with the first epidemic peak appears in June in each of the four regions; the second epidemic appears in October, but mainly in the southern region (Ho et al., 1999). In this study, the highest incidence rate occurred in the southern region might be the temperature associated. The temperature is generally higher in the southern region than in the other regions. The incidence rate reaches to a peak in October in southern region during the year. The southern region is the area with an average temperature exceeded 25℃ in October (Figure 10). This may explain why the southern region has an elevated incidence rate of the infection in October.

5.5 Enteroviral infection associate with weather status

Since May to October are fragment months for the epidemic of HFMD and herpangina, we expect a relationship between the epidemic and weather, particularly with the temperature. The study in Japan has shown that the cases of HFMD and herpangina is associated with the increase of the daily average temperature. They also found that the cases of HFMD and herpangina increases while the vapor pressure is over 15hPa. But other study suggested that there is no obvious linear relationship between cases and the weather parameters (Urashima et al. 2003)

In our study, the risk of complications from the enteroviral infection increases as

the daily average temperature increases, and sunshine hours increase in the univariate analysis of Poisson regression model. In the multivariate analysis including both temperature and sunshine hours in the model, however, the sunshine hours do not predict the enteroviral severe infection. On the other hand, temperature is not a significant factor associated with the complication cases if months are included in the multivariate model. The month in a year is a stronger indicator than specific temperature as independent variable associated with the epidemic.

We found that the reported rate of HFMD and herpangina increases as the average daily maximum temperature increases. The multivariate analysis reveals the inverse association between the precipitation and HFMD and herpangina probably reflects the temperature association. The association with the sunshine hours is also in collinearity with the average maximum temperature. The incidence of severe cases of enteroviral infection reached to the level of 12.7 per 100,000 in 2001 after the largest outbreak in 1998. The incidence declined continually to 1.79 per 100,000 in 2004 and 0.43 per 100,000 in 2006. Another large epidemic is occurring in 2008. As of July 10, 2008, 324 severe cases were reported.

5.6 Enterovirus infection associated with virology tested

The chronological epidemic curve of enterovirus infection demonstrates that a

larger epidemic may occur every few years in Taiwan. The data also show that younger children are at the higher risk than older children. This type of epidemic is a typical phenomenon associated with herd immunity.

Chang et al. (2002) found that the age-specific sero-positive rate of enteovirus infection was the lowest in children younger than 3 years of age, followed by children of 3-12 years old and the highest in the older children. Their study shows that the young children have the lowest rate of antibody with the highest rate of severe and fatal cases in the EV71 epidemic. This inverse sero-positive association with age alarms when a larger epidemic may occurs. Adequate surveillance of sero-test may predict the epidemic.

Chapter 6: Conclusion

The seasonal variation of enteroviral infection was distinctive in Taiwan. The epidemic is associated with both the weather and school activities well; the risk of infection decreases while children have no school in the winter and summer breaks. The monthly variations of the incidence by area show that the epidemic may spread from other areas to the south. The higher temperature in the fall may attribute to the second wave of infection in the Southern Taiwan.

The complication of severe cases from the virus infection that cause HFMD and herpangina are not alike between Southern Taiwan and the other regions. The mechanism remain unclear. The association with ecological factors, weather and socio-economic status deserves more studies.

Table 1 Numbers of reported and confirmed enteroviral severe cases by age and gender in 2000-2004, Taiwan

	Boys		Girls		Total	
	Reported	Confirmed (%)	Reported	Confirmed (%)	Reported	Confirmed (%)
<1 year	226	123 (54.4)	124	75 (60.5)	350	198 (56.6)
1-	280	188 (64.3)	180	110 (61.1)	460	298 (64.8)
2-	178	122 (68.5)	134	87 (64.9)	312	209 (67.0)
3-	94	63 (67.0)	78	45 (57.7)	172	108 (62.8)
4-	82	46 (56.1)	48	28 (58.3)	130	74 (56.9)
5-9	88	36 (40.9)	61	25 (41.0)	149	61 (40.9)
total	948	578 (61.0)	625	370 (59.2)	1573	948 (60.3)

Table 2 Incidence rates of confirmed enteroviral severe cases by age and gender in 2000-2004, Taiwan

	Boys		Girls		Total	
	case	incidence rate	case	incidence rate	case	incidence rate
<1 year	123	19.24	75	12.86	198	16.20
1-	188	27.09	110	17.31	298	22.41
2-	122	16.84	87	13.09	209	15.04
3-	63	8.27	45	6.44	108	7.40
4-	46	5.88	28	3.89	74	4.92
5-9	36	0.87	25	0.66	61	0.77
total	578	7.47	370	5.20	948	6.39

Incidence rate=(cases/population)*100000

Table 3 Confirmed enteroviral severe cases by age and region in 2000-2004, Taiwan

	Region				Total
	Northern	Central	Southern	Eastern	
	n (%)	n (%)	n (%)	n (%)	n (%)
<1 year	63 (23.5)	49 (19.7)	81 (19.9)	5 (20.8)	198 (20.9)
1-	77 (26.1)	86 (34.5)	127 (31.2)	8 (33.3)	298 (31.4)
2-	49 (18.3)	60 (24.1)	96 (23.6)	4 (16.7)	209 (22.0)
3-	32 (11.9)	31 (12.4)	44 (10.8)	1 (4.2)	108 (11.4)
4-	18 (6.7)	14 (5.6)	39 (9.6)	3 (12.5)	74 (7.8)
5-9	29 (10.8)	9 (3.6)	20 (4.9)	3 (12.5)	61 (6.4)
total	268 (100)	249 (100)	407 (100)	24 (100)	948 (100)

Table 4 Incidence rate of confirmed enteroviral severe cases by age and region in 2000-2004, Taiwan

	Region				Total
	Northern	Central	Southern	Eastern	
<1 year	11.95	17.09	21.54	15.26	16.20
1-	13.37	27.57	31.30	22.39	22.41
2-	8.11	18.44	22.70	10.75	15.04
3-	5.02	9.09	9.94	2.57	7.40
4-	2.73	4.00	8.62	7.57	4.92
5-9	0.82	0.49	0.85	1.49	0.77
total	4.10	7.19	9.13	6.22	6.39

Incidence rate= (cases/population)*100000

Table 5 Univariate Poisson regression analysis for enteroviral severe cases associated with gender, age and region

Variables	n	Rate	RR	95% CI	P value
Gender					
Boy	578	7.47	1.44	1.26-1.64	<0.0001
Girl	370	5.20	1.00		
Age					
<1year	198	16.20	21.1	15.8-28.1	<0.0001
1-	298	22.41	29.2	22.2-38.4	<0.0001
2-	209	15.04	19.6	14.7-26.1	<0.0001
3-	108	7.40	9.62	7.03-13.2	<0.0001
4-	74	4.92	6.41	4.57-8.99	<0.0001
5-9	61	0.77	1.00		
Region					
Northern	268	4.10	1.00		
Central	149	7.19	1.75	1.48-2.08	<0.0001
Southern	407	9.13	2.23	1.91-2.60	<0.0001
Eastern	24	6.22	1.52	0.99-2.30	0.0504

Rate: per 100,000
RR, relative risk; CI, confidence interval.

Table 6 Univariate Poisson regression analysis for enteroviral severe cases associated with chronological year, season and month

Variables	n	Rate	RR	95% CI	P value
Year					
2000	283	9.58	5.11	3.78-6.90	<0.0001
2001	388	12.73	7.11	5.30-9.54	<0.0001
2002	159	5.75	2.98	2.17-4.09	<0.0001
2003	68	2.41	1.31	0.91-1.89	0.1544
2004	50	1.79	1.00		
Season					
Spring	222	14.95	2.04	1.62-2.56	<0.0001
Summer	334	22.50	3.06	2.47-3.80	<0.0001
Autumn	283	19.06	2.60	2.08-3.24	<0.0001
Winter	109	7.34	1.00		
Month					
1	42	2.83	2.08	1.15-3.75	0.0149
2	15	1.01	1.00		
3	29	1.95	1.47	0.79-2.75	0.2236
4	66	4.45	2.65	1.51-4.65	0.0007
5	127	8.55	5.10	2.99-8.71	<0.0001
6	139	9.36	5.58	3.28-9.51	<0.0001
7	99	6.67	3.98	2.31-6.85	<0.0001
8	96	6.47	3.86	2.24-6.65	<0.0001
9	94	6.33	3.78	2.19-6.51	<0.0001
10	114	7.68	4.58	2.67-7.85	<0.0001
11	75	5.05	3.01	1.73-5.25	<0.0001
12	52	3.50	2.09	1.18-3.71	0.0019

Rate: per 100,000 ; per 1,000,000 in season and month
RR, relative risk; CI, confidence interval.

Table 7 Univariate Poisson regression analysis for enteroviral severe cases associated with weather parameters

Variables	RR	95% CI	P value
Average daily temperature			
<15℃	1.00		
15-19.9	1.07	0.60-1.94	0.8124
20-24.9	2.20	1.26-3.84	0.0056
25-29.9	3.71	2.14-6.42	<0.0001
≧30	0.26	0.03-1.96	0.1891
Daily maximum temperature			
<15℃	1.00		
15-19.9	1.17	0.28-4.94	0.8297
20-24.9	1.23	0.30-4.98	0.7724
25-29.9	2.77	0.69-11.1	0.1514
≧30	3.36	0.84-13.5	0.0870
Daily minimum temperature			
<10℃	1.00		
10-14.9	0.62	0.09-4.48	0.6336
15-19.9	0.78	0.11-5.54	0.7998
20-24.9	2.04	0.29-14.5	0.4761
≧25	1.86	0.26-13.3	0.5347
Average daily rainfall hours			
0-4.9 hrs	1.00		
5-9.9	1.03	0.86-1.24	0.7615
10-14.9	1.36	1.00-1.86	0.0506
15-19.9	1.25	0.59-2.62	0.5617
≧20	1.25	0.31-5.02	0.7502
Average daily sunshine hours			
0-2.49 hrs	1.45	1.19-1.77	0.0002
2.50-4.99	1.00		
5.00-7.49	1.26	1.04-1.53	0.0188
7.50-9.99	1.69	1.40-2.04	<0.0001
≧10	1.84	1.33-2.54	0.0002

RR, relative risk; CI, confidence interval.

Table 8 Multivariate Poisson regression analysis for factors associated with enteroviral severe cases

Variables	n	Rate	RR	95%CI	P value
Gender					
Boys	578	7.47	1.43	1.26-1.63	<0.0001
Girls	370	5.20	1.00		
Age					
<1 year	198	16.20	20.9	15.7-27.8	<0.0001
1-	298	22.41	28.9	22.0-38.1	<0.0001
2-	209	15.04	19.4	14.6-25.8	<0.0001
3-	108	7.40	9.57	6.99-13.1	<0.0001
4-	74	4.92	6.39	4.55-9.0	<0.0001
5-9	61	0.77	1.00		
Region					
Northern	268	4.10	1.00		
Central	149	7.19	1.67	1.40-1.98	<0.0001
Southern	407	9.13	2.02	1.72-2.37	<0.0001
Eastern	24	6.22	1.38	0.91-2.11	0.1279
Month					
1	42	2.83	2.59	1.43-4.68	0.0016
2	15	1.01	1.00		
3	29	1.95	1.68	0.90-3.17	0.1055
4	66	4.45	3.25	1.78-5.93	<0.0001
5	127	8.55	5.08	2.78-9.29	<0.0001
6	139	9.36	5.50	3.00-10.1	<0.0001
7	99	6.67	4.74	2.01-6.99	<0.0001
8	96	6.47	3.61	1.94-6.72	<0.0001
9	94	6.33	3.67	1.97-6.82	<0.0001
10	114	7.68	5.14	2.84-9.29	<0.0001
11	75	5.05	4.23	2.37-7.55	<0.0001
12	52	3.50	3.11	1.75-5.53	<0.0001
Daily average temperature					
<15℃			1.00		
15-19.9			0.99	0.58-1.71	0.9797
20-24.9			1.10	0.62-1.94	0.7505
25-29.9			1.68	0.91-3.08	0.0976
≧30			1.48	0.72-3.06	0.2812

Rate: 100,000 for gender, age, and region
RR, relative risk; CI, confidence interval.

Table 9 Multivariate Poisson regression analysis for factors associated with enteroviral severe cases

Variables		RR	95% CI	P value
Gender				
	Boys	1.43	1.26-1.63	<0.0001
	Girls	1.00		
Age				
	<1 year	20.9	15.6-27.8	<0.0001
	1-	28.9	21.9-38.1	<0.0001
	2-	19.4	14.6-25.8	<0.0001
	3-	9.57	6.99-13.1	<0.0001
	4-	6.39	4.55-8.96	<0.0001
	5-9	1.00		
Region				
	Northern	1.00		
	Central	1.67	1.40-1.99	<0.0001
	Southern	1.96	1.67-2.29	<0.0001
	Eastern	1.31	0.86-1.99	0.2037
Daily average temperature				
	<15℃	1.00		
	15-19.9	1.13	0.66-1.93	0.6538
	20-24.9	1.86	1.11-3.11	0.0180
	25-29.9	3.66	2.21-6.06	<0.001
	≧30	3.19	1.70-5.98	0.0003
Daily average sunshine hours				
	0-2.49 hrs	1.00		
	2.50-4.99	0.91	0.74-1.12	0.3873
	5.00-7.49	0.77	0.64-0.95	0.0115
	7.50-9.99	0.84	0.70-1.01	0.0626
	≧10	0.83	0.65-1.06	0.1422

RR, relative risk; CI, confidence interval.

Table 10 Annual sentinel physicians reported cases of HFMD and herpangina in 2000-2004, Taiwan

Year	physicians reported	pop	Rate (per 10^3)
2000	135565	22035847	6.15
2001	111486	22187051	5.02
2002	93048	22304062	4.17
2003	94764	22401571	4.23
2004	97002	22483004	4.31
Total	531865	111411535	4.77

Table 11 Sentinel physicians reported cases of HFMD and herpangina by region in 2000-2004, Taiwan

Region	physicians reported	pop	Rate (per 10^3)
Northern	129960	48569455	2.68
Central	158480	24546343	6.46
Southern	215355	35312433	6.10
Eastern	28070	2983304	9.41
Total	531865	111411535	4.77

Table12 Multivariate Poisson regression analysis for risk of sentinel physicians reported HFMD and herpangina associated with region, chronological year and month

Variables		RR	95% CI	P value
Region				
	Northern	1.00		
	Central	2.41	2.39-2.43	<0.0001
	Southern	2.28	2.26-2.29	<0.0001
	Eastern	3.51	3.46-3.55	<0.0001
Year				
	2000	1.47	1.46-1.48	<0.0001
	2001	1.20	1.19-1.21	<0.0001
	2002	1.00		
	2003	1.02	1.01-1.02	0.0012
	2004	1.04	1.03-1.05	<0.0001
Month				
	1	1.49	1.46-1.52	<0.0001
	2	1.00		
	3	1.73	1.70-1.77	<0.0001
	4	3.77	3.70-3.84	<0.0001
	5	6.48	6.37-6.60	<0.0001
	6	6.11	6.01-6.22	<0.0001
	7	3.46	3.40-3.53	<0.0001
	8	2.42	2.37-2.46	<0.0001
	9	2.66	2.61-2.71	<0.0001
	10	2.63	2.58-2.68	<0.0001
	11	2.60	2.55-2.65	<0.0001
	12	2.08	2.04-2.12	<0.0001

RR, relative risk; CI, confidence interval.

Table 13 Multivariate Poisson regression analysis for risk of sentinel physicians reported HFMD and herpangina associated with region, chronological year, temperature, rainfall and sunshine

Variables	RR	95% CI	P value
Region			
Northern	1.00		
Central	2.31	2.29-2.33	<0.0001
Southern	1.94	1.92-1.95	<0.0001
Eastern	3.14	3.10-3.18	<0.0001
Year			
2000	1.52	1.50-1.53	<0.0001
2001	1.24	1.23-1.25	<0.0001
2002	1.00		
2003	1.07	1.06-1.08	<0.0001
2004	1.10	1.09-1.11	<0.0001
Weekly maximum temperature			
<15℃	1.00		
15-19.9	1.67	1.48-1.90	<0.0001
20-24.9	2.58	2.27-2.92	<0.0001
25-29.9	4.88	4.30-5.54	<0.0001
≧30	6.39	5.64-7.25	<0.0001
Average weekly rainfall hours			
0-4.9 hrs	1.69	1.45-1.97	<0.0001
5-9.9	1.59	1.36-1.85	<0.0001
10-14.9	1.80	1.54-2.10	<0.0001
≧15	1.00		
Average weekly sunshine hours			
0-2.49 hrs	1.00		
2.5-4.99	0.88	0.87-0.89	<0.0001
5.0-7.49	0.81	0.80-0.82	<0.0001
7.5-9.99	0.79	0.78-0.80	<0.0001
≧10	0.74	0.73-0.77	<0.0001

RR, relative risk; CI, confidence interval.

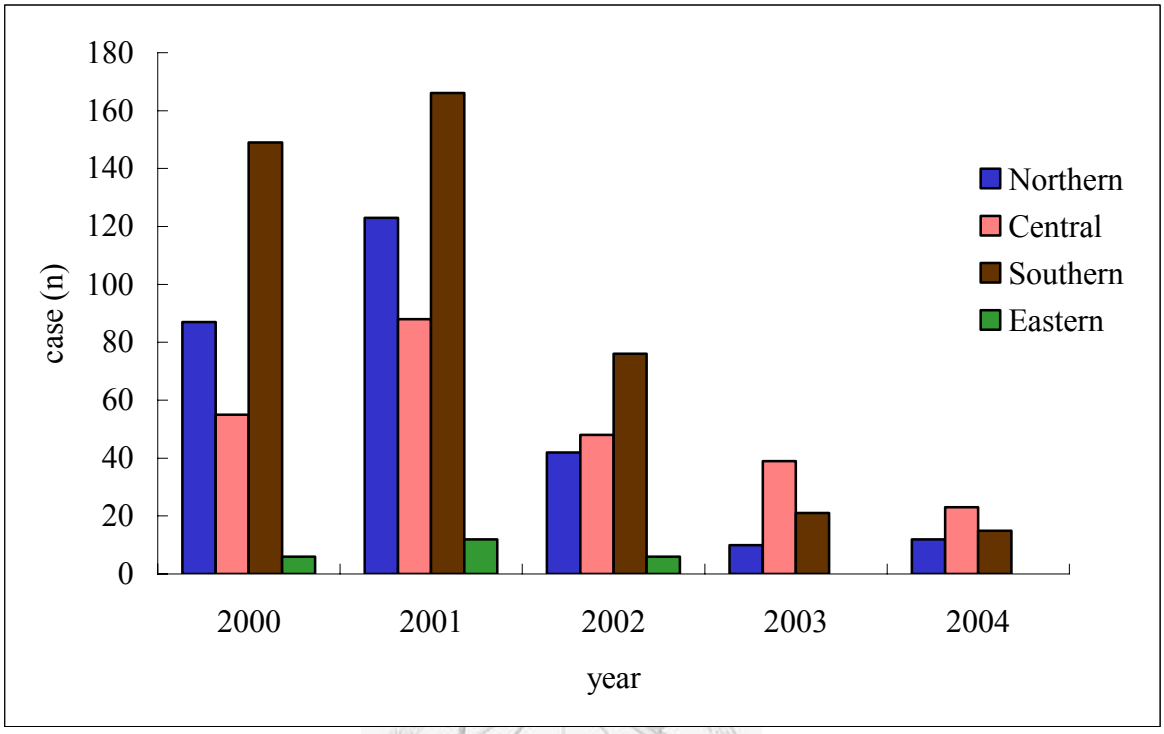

Figure 1- 1 Annual cases of confirmed severe complication of enteroviral infection disease by region in 2000-2004 in Taiwan

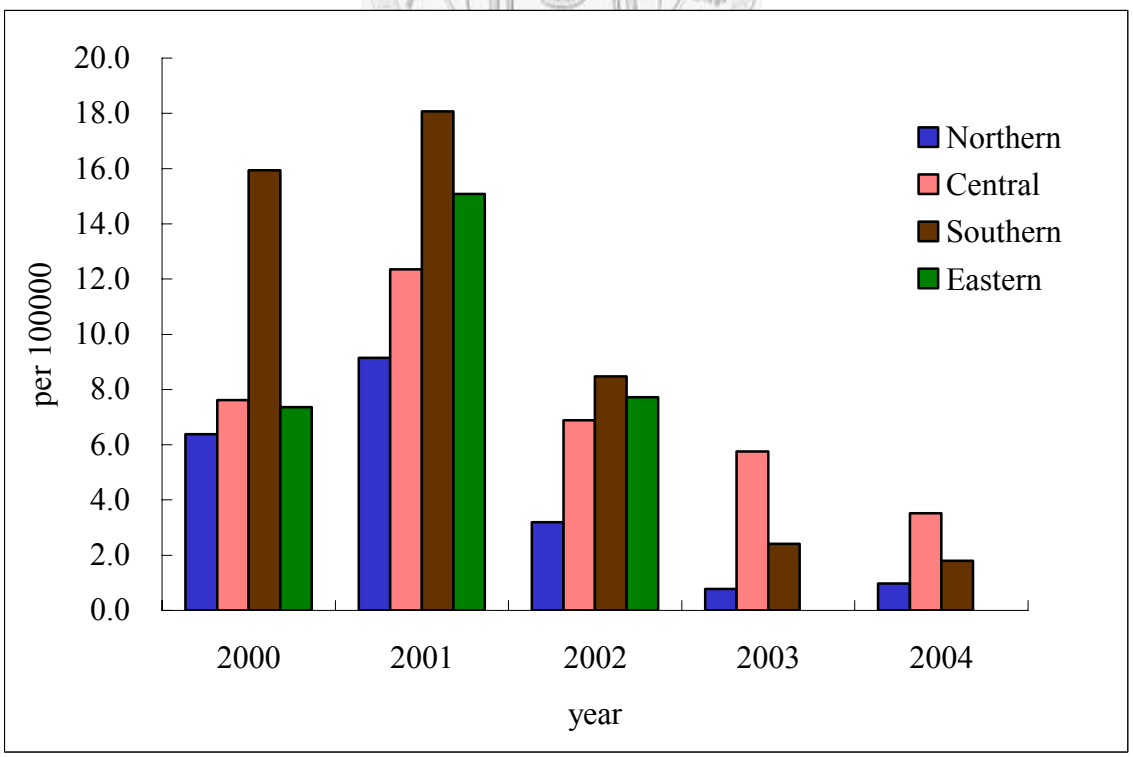

Figure 1- 2 Annual incidence rates of confirmed severe complication of enteroviral infection by region in 2000-2004 in Taiwan

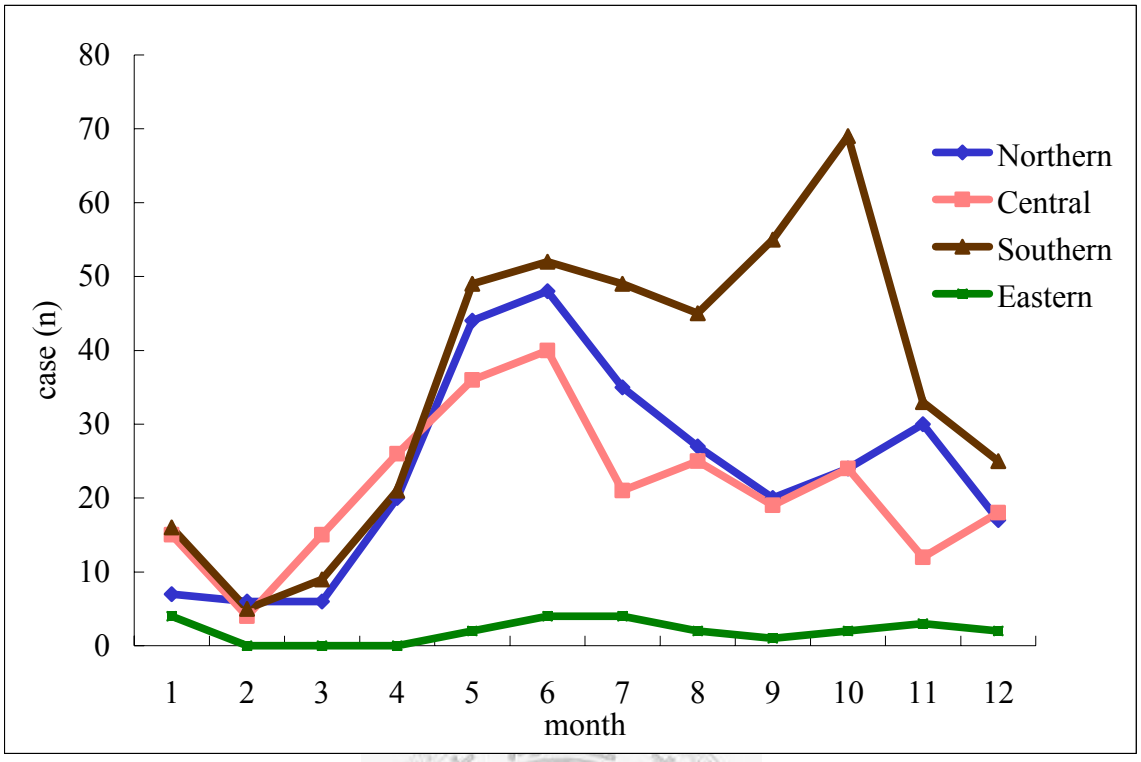

Figure 2- 1 Overall monthly severe complication of enteroviral infection by region in 2000-2004, Taiwan

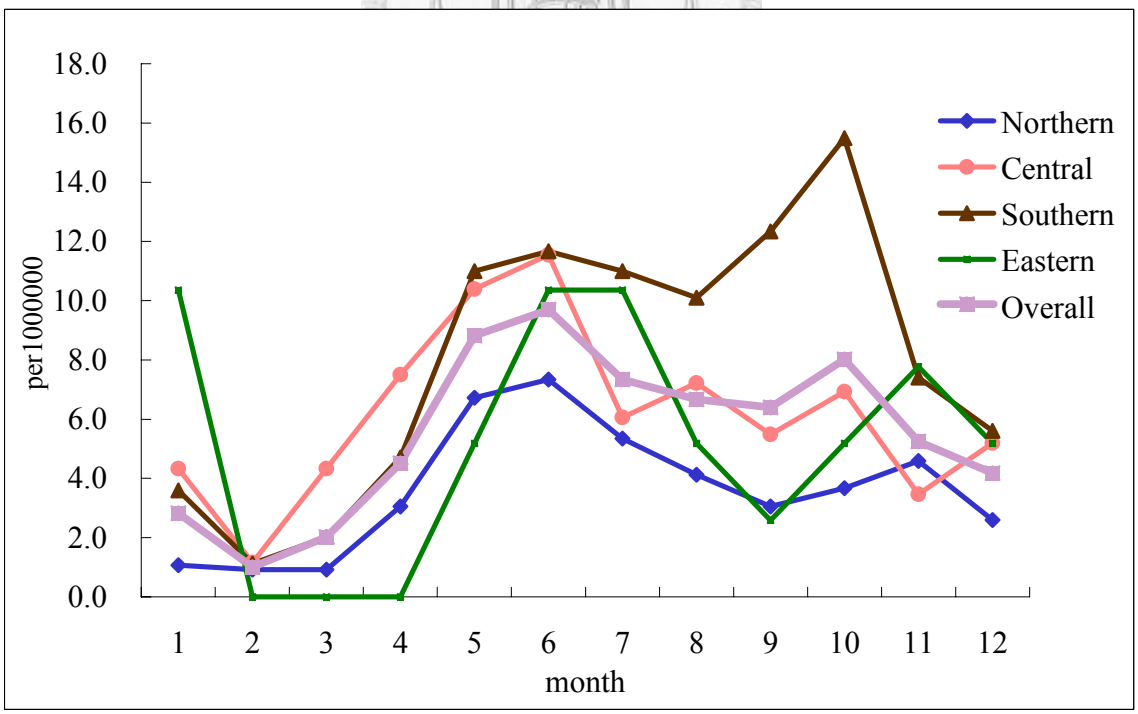

Figure 2- 2 Monthly incidence rates of severe complication from enteroviral infection by region in 2000-2004, Taiwan

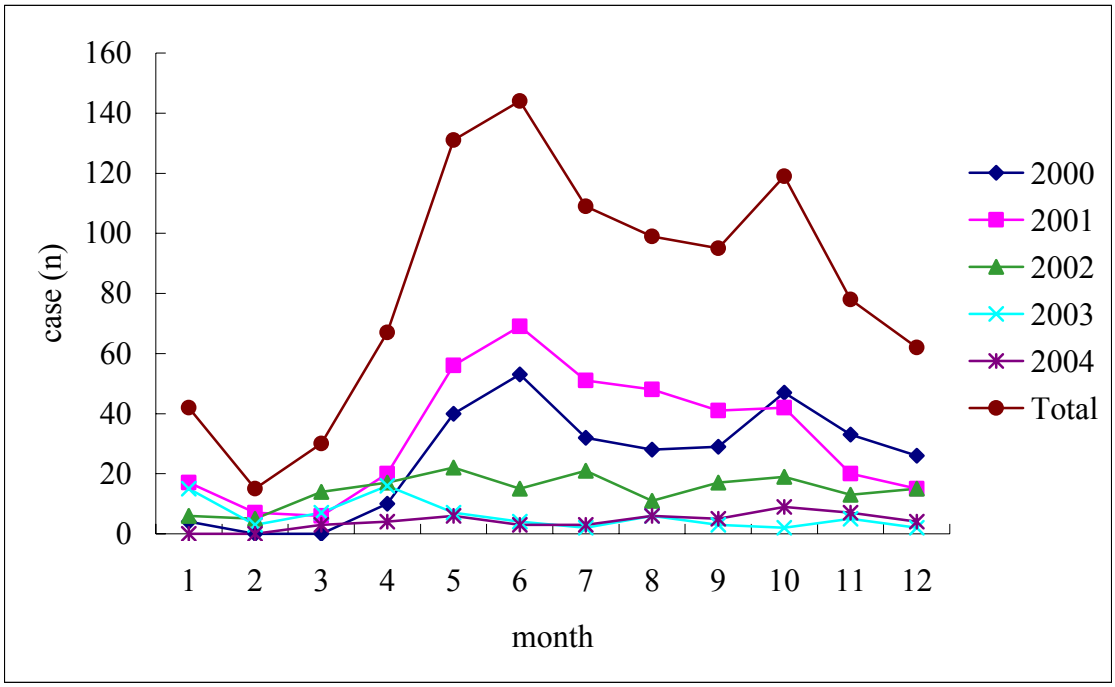

Figure 3- 1 Monthly cases of severe enteroviral disease by year in 2000-2004, Taiwan

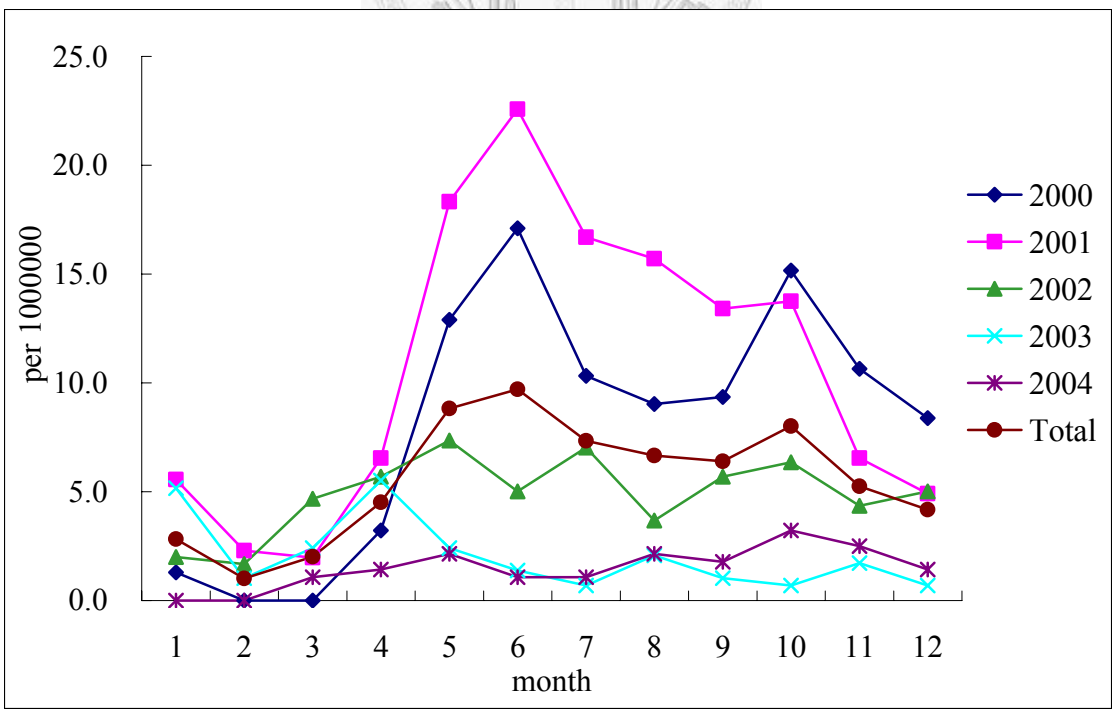

Figure 3- 2 Monthly incidence rate of severe enteroviral disease by year in 2000-2004, Taiwan

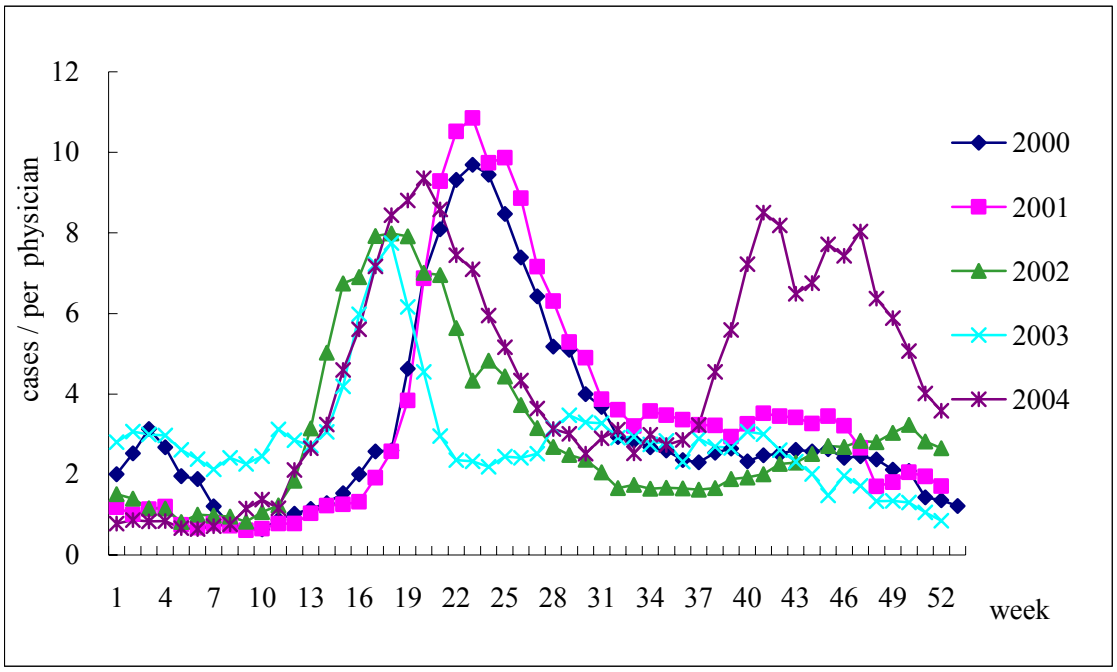

Figure 4 Weekly average cases of HFMD and herpangina reported per sentinel physician at hospitals by year in 2000-2004, Taiwan

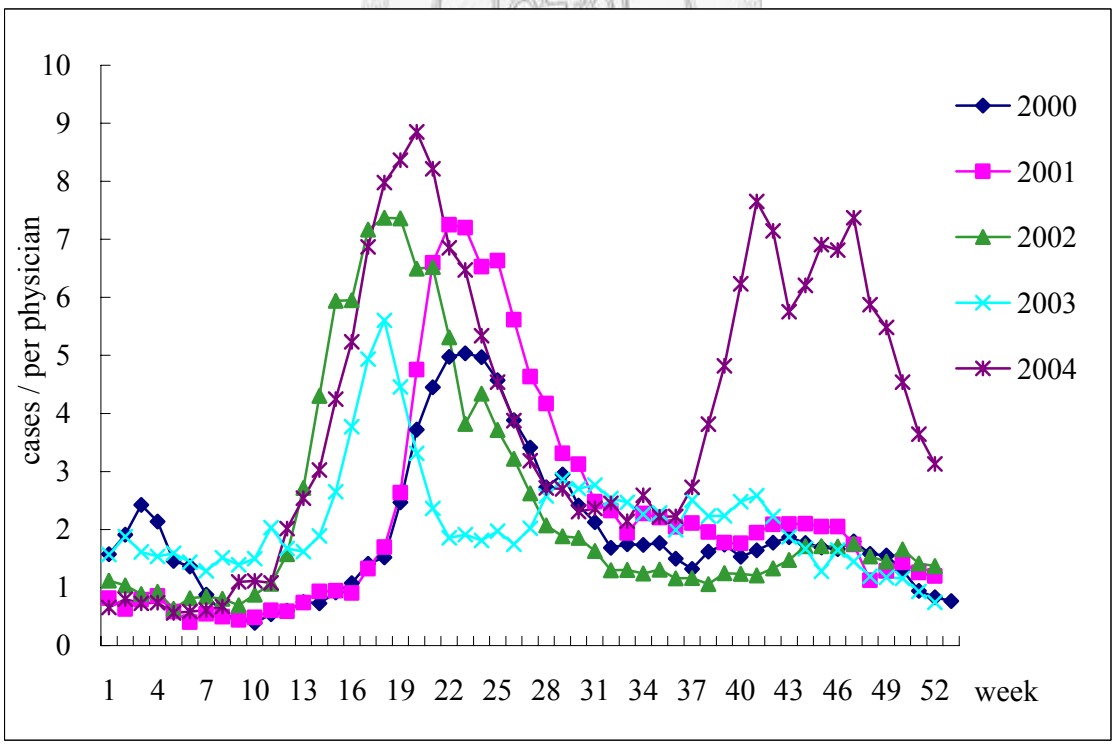

Figure 5- 1 Weekly average cases of herpangina reported per sentinel physician at hospitals in 2000-2004, Taiwan

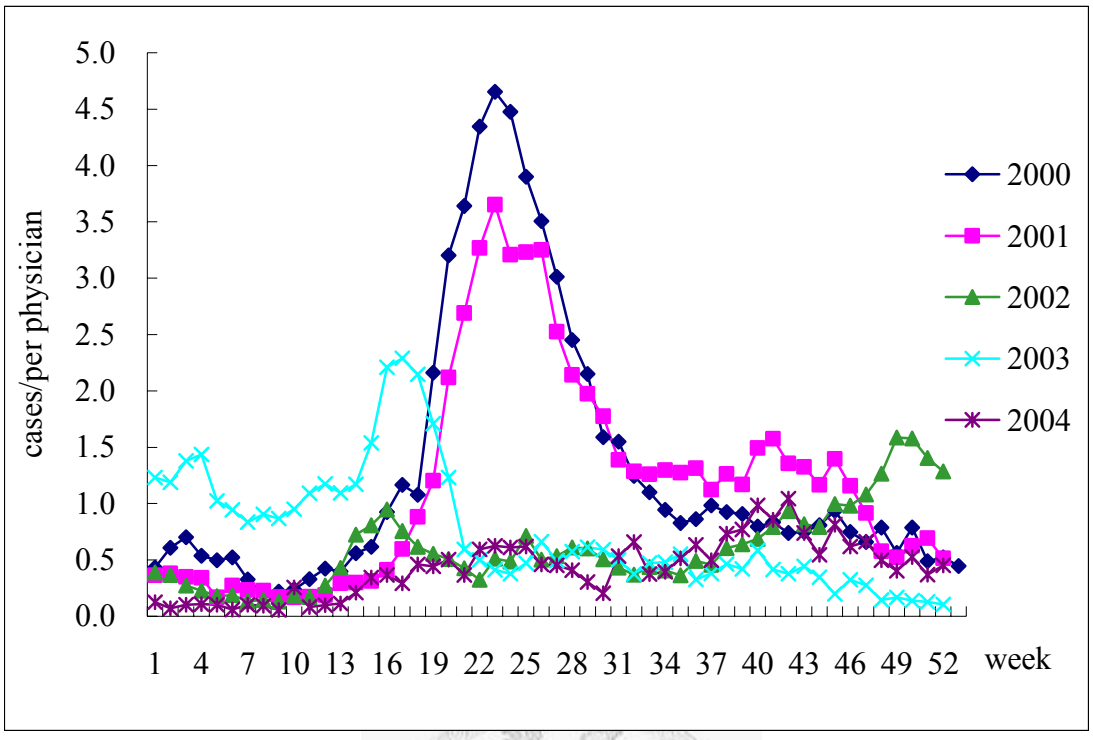

Figure 5- 2 Weekly average cases of HFMD reported per sentinel physician at hospitals in 2000-2004, Taiwan

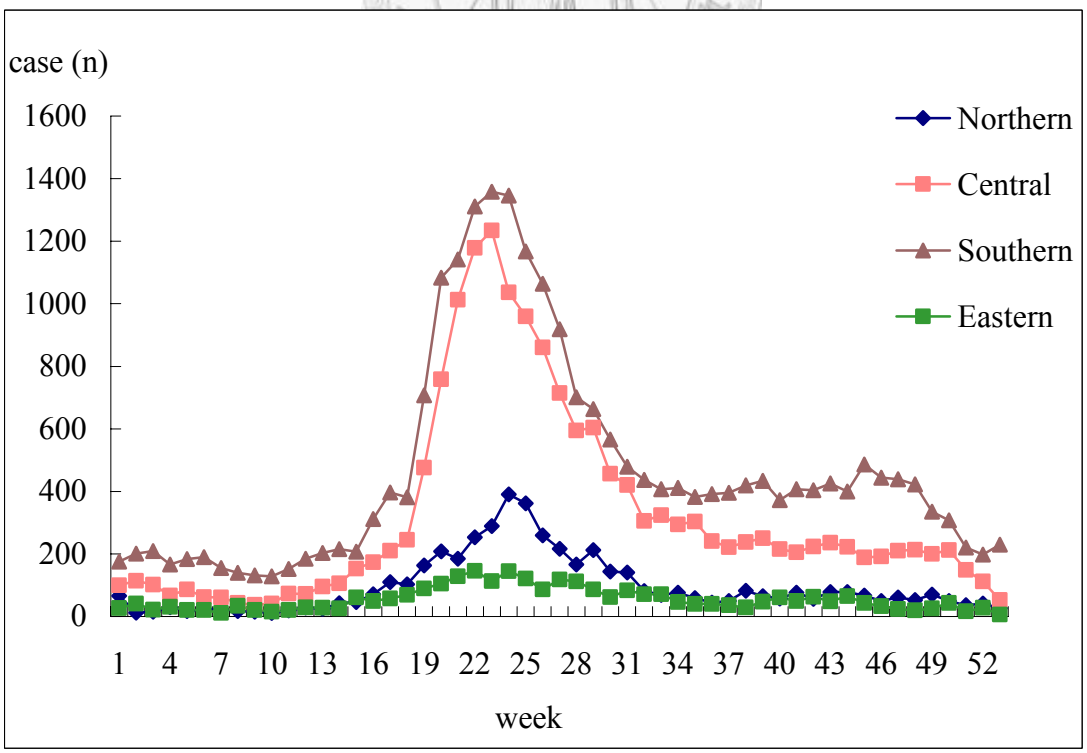

Figure 6- 1 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at hospitals in 2000, Taiwan

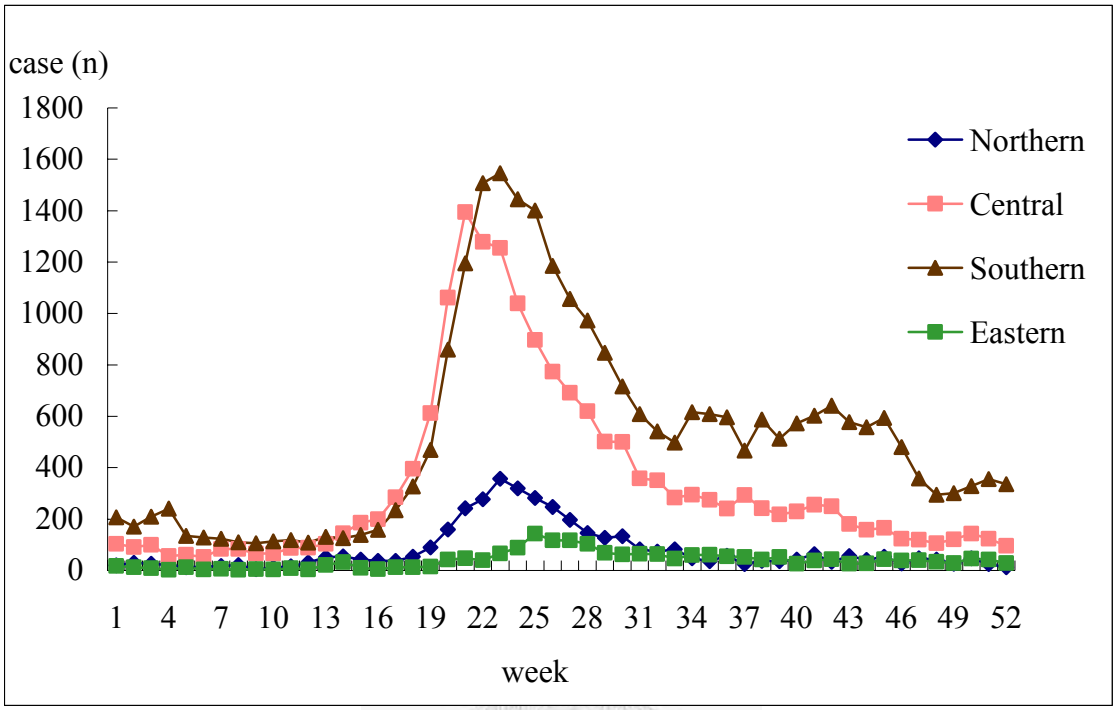

Figure 6- 2 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at hospitals in 2001, Taiwan

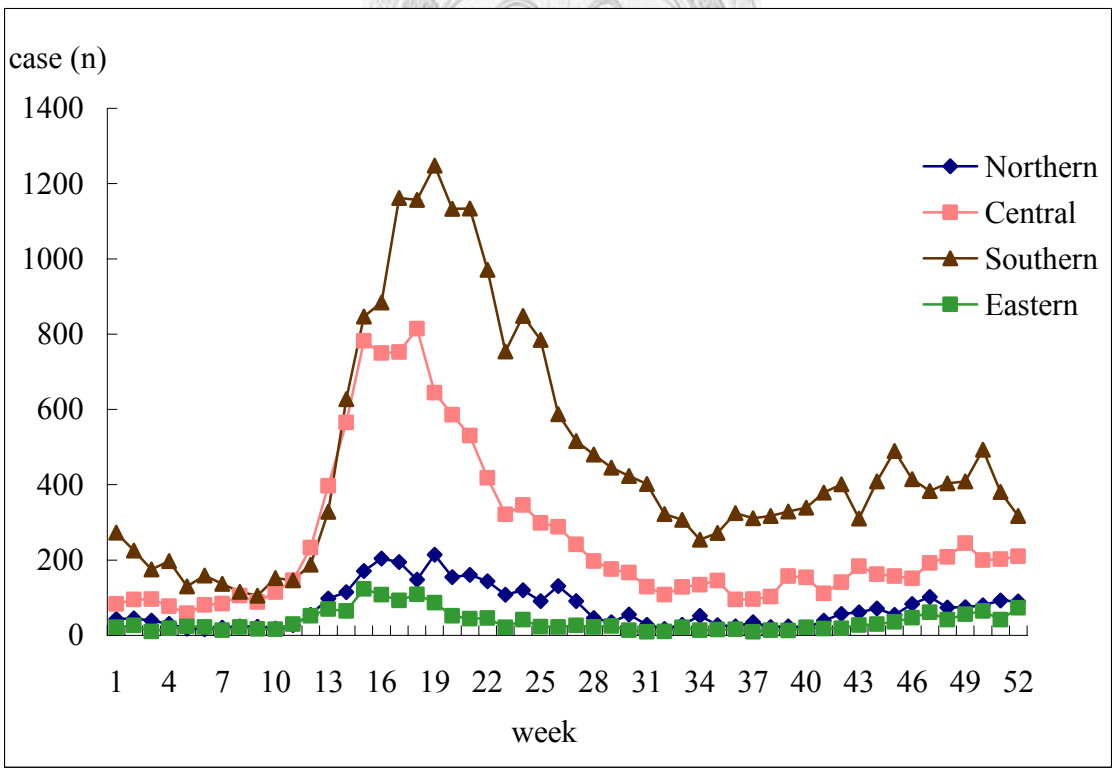

Figure 6- 3 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at hospitals in 2002, Taiwan

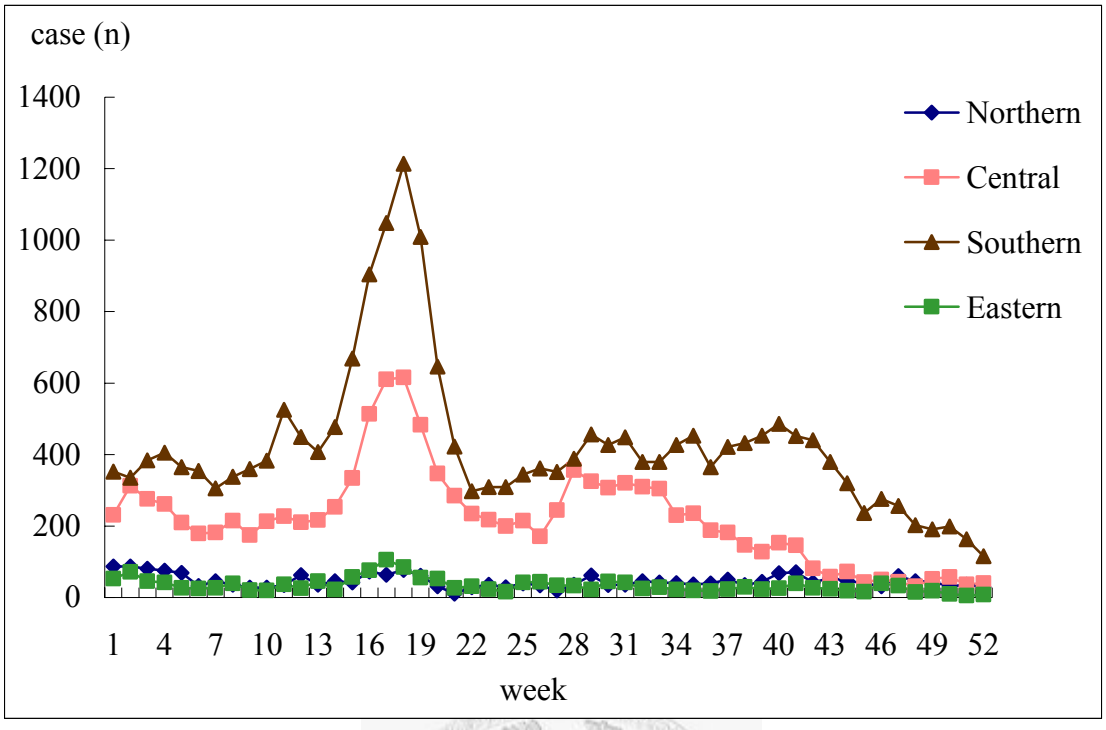

Figure 6- 4 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at hospitals in 2003, Taiwan

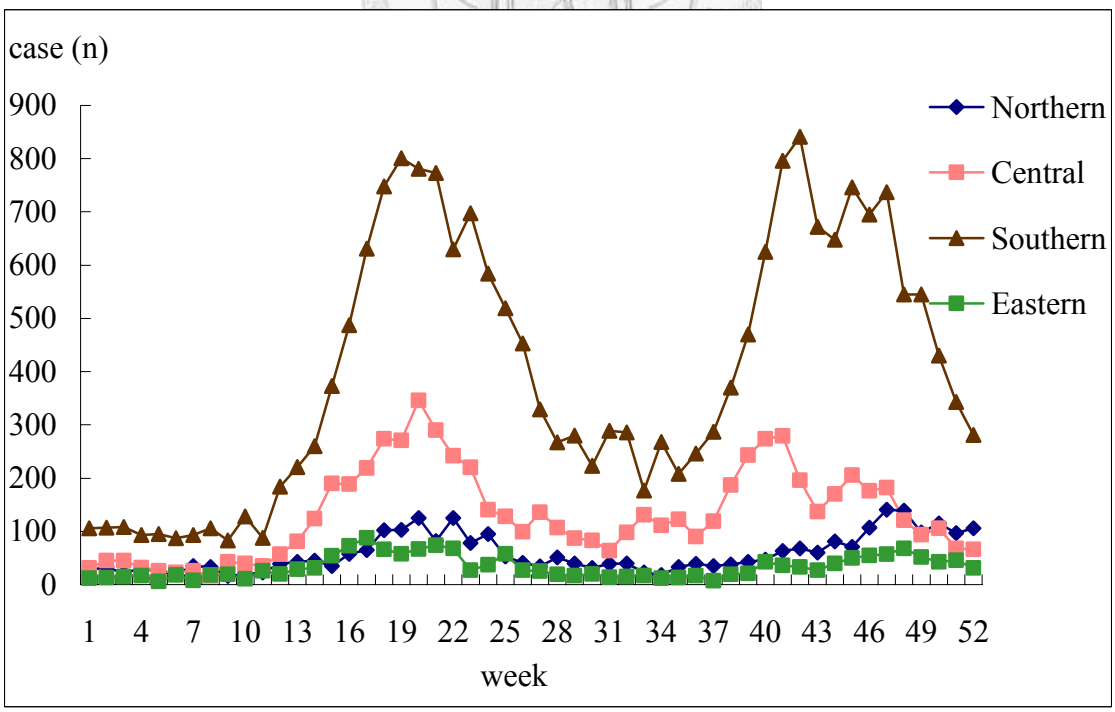

Figure 6- 5 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at hospitals in 2004, Taiwan

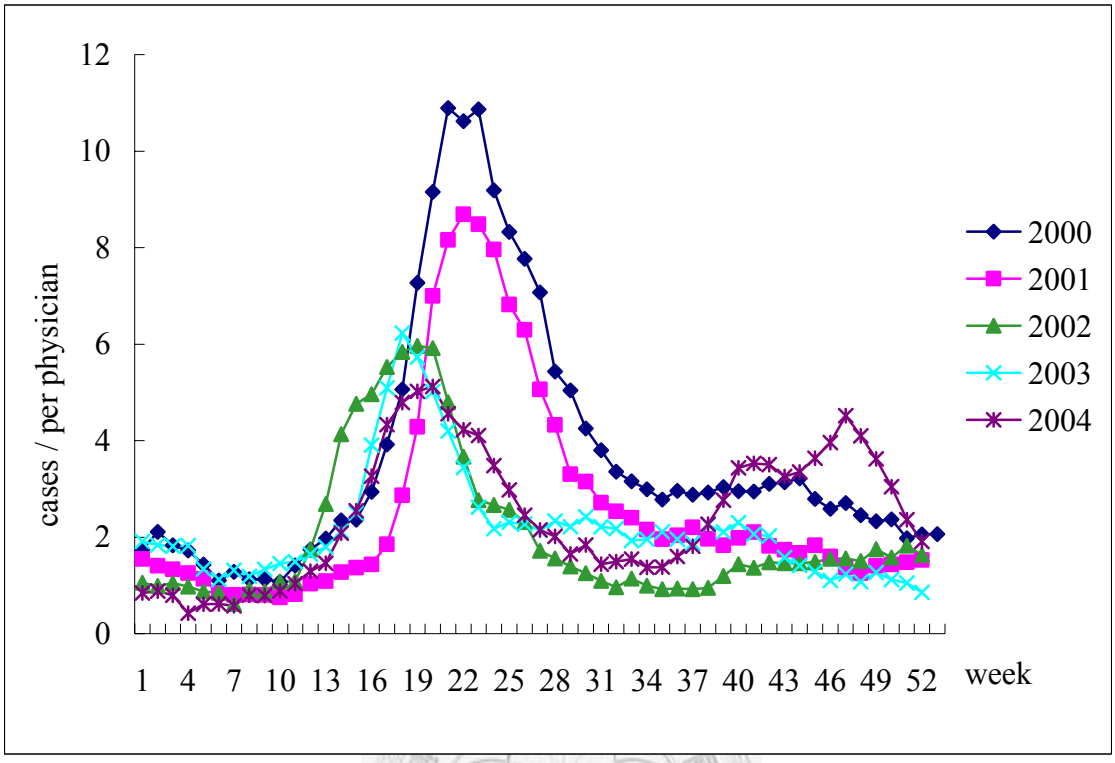

Figure 7 Weekly average cases of HFMD and herpangina reported per sentinel physicians at clinics by year in 2000-2004, Taiwan

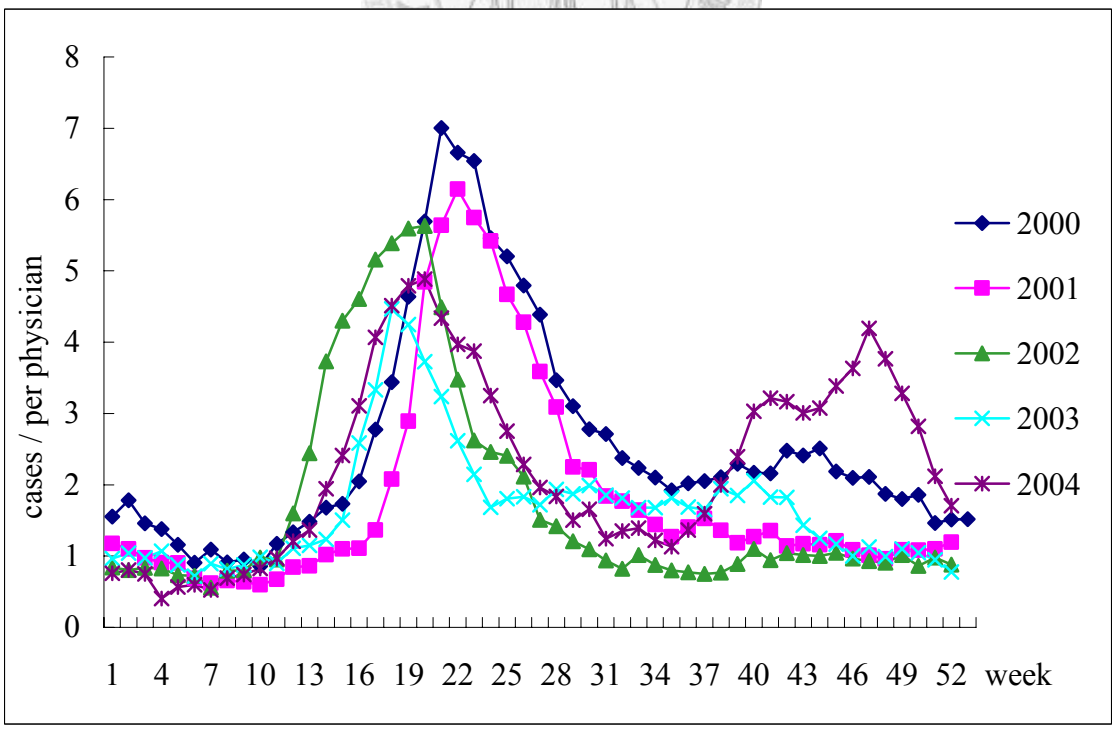

Figure 8- 1 Weekly average cases of herpangina reported per sentinel physicians at clinics by year in 2000-2004, Taiwan

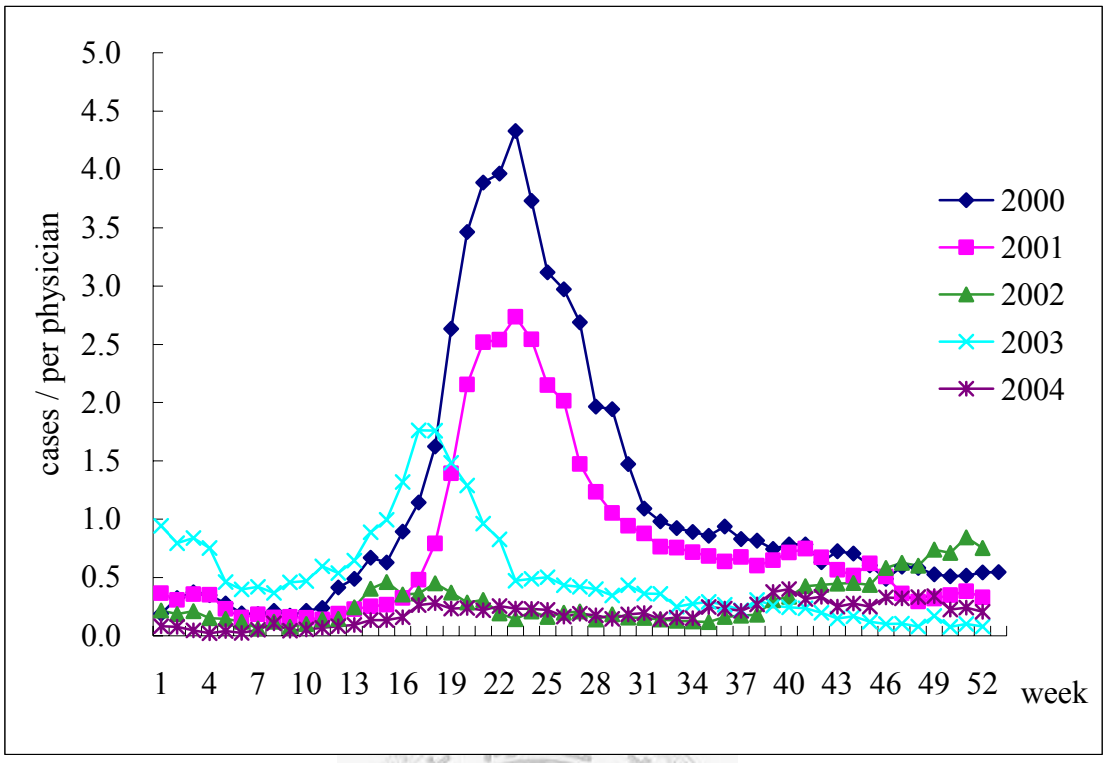

Figure 8- 2 Weekly average cases of HFMD reported per sentinel physicians at clinics by year in 2000-2004, Taiwan

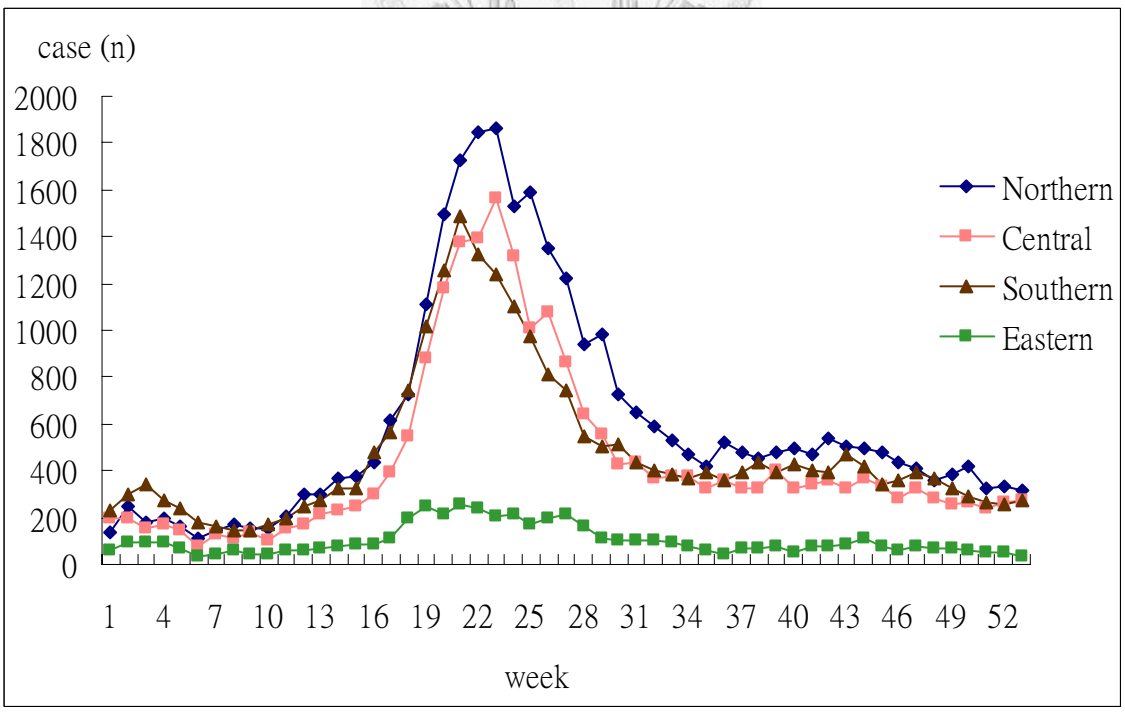

Figure 9- 1 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at clinics in 2000, Taiwan

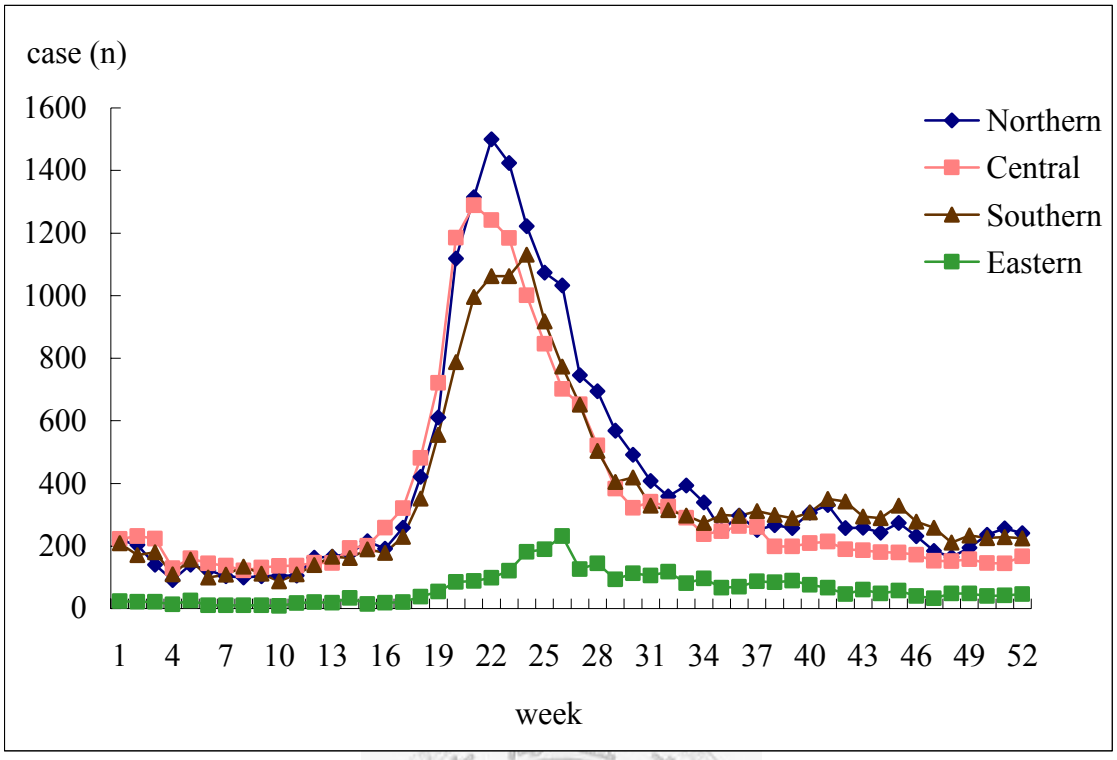

Figure 9- 2 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at clinics in 2001, Taiwan

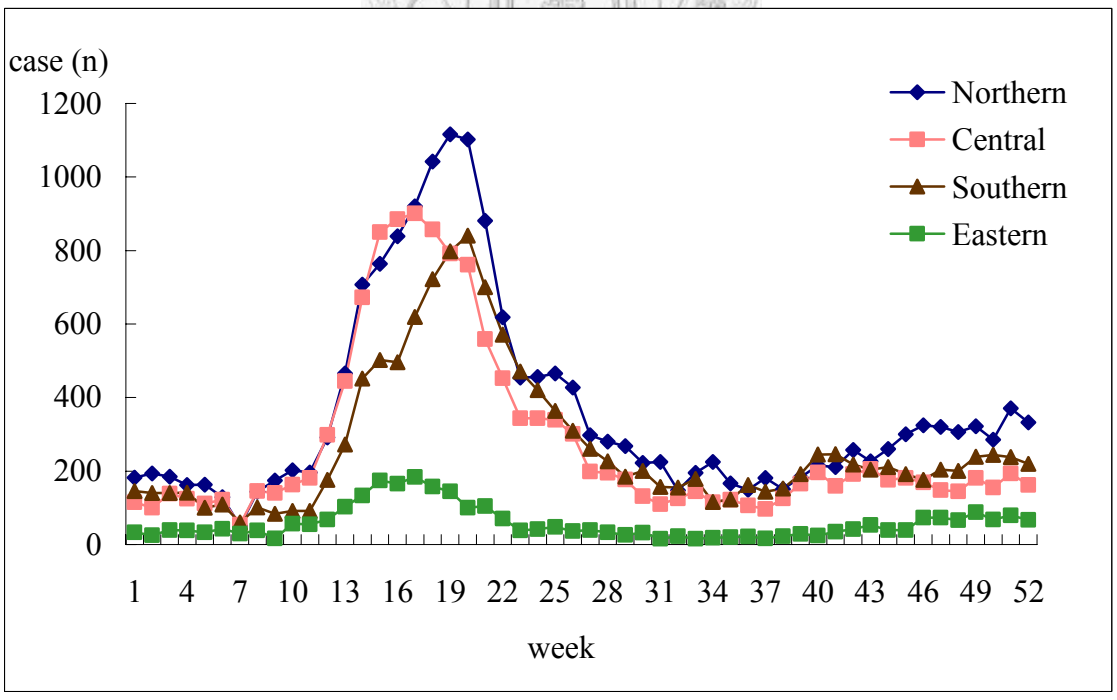

Figure 9- 3 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at clinics in 2002, Taiwan

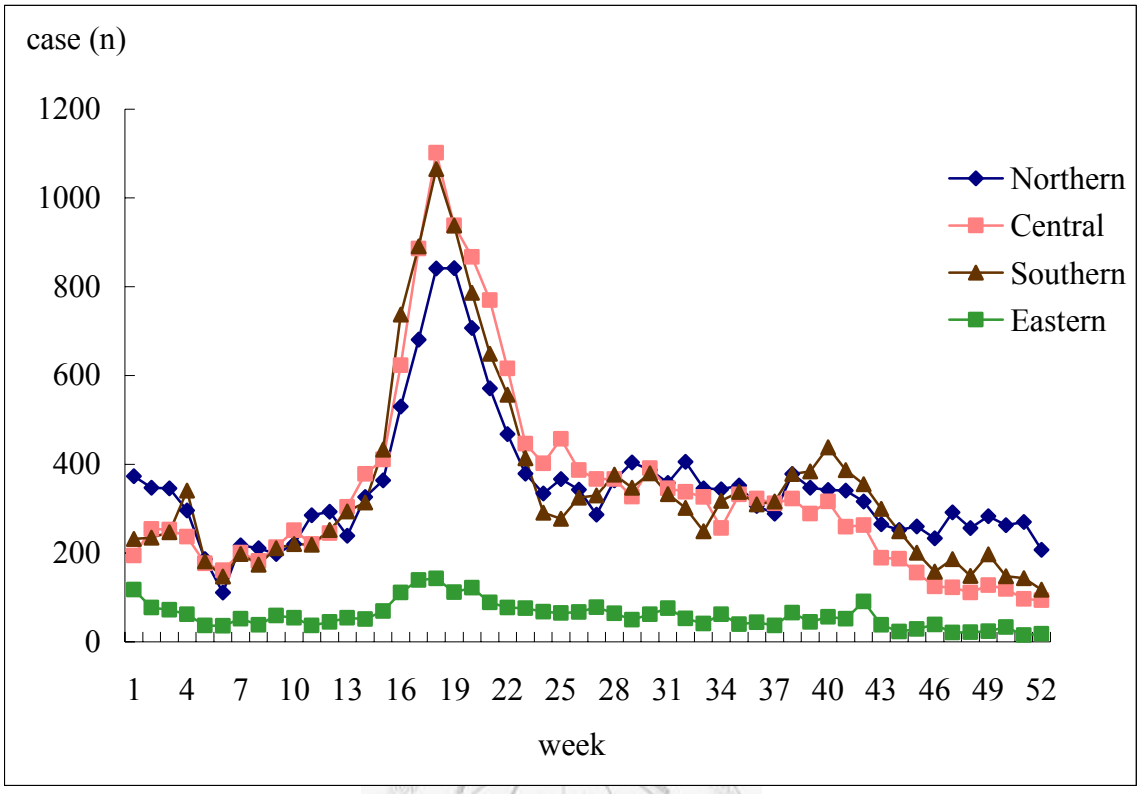

Figure 9- 4 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at clinics in 2003, Taiwan

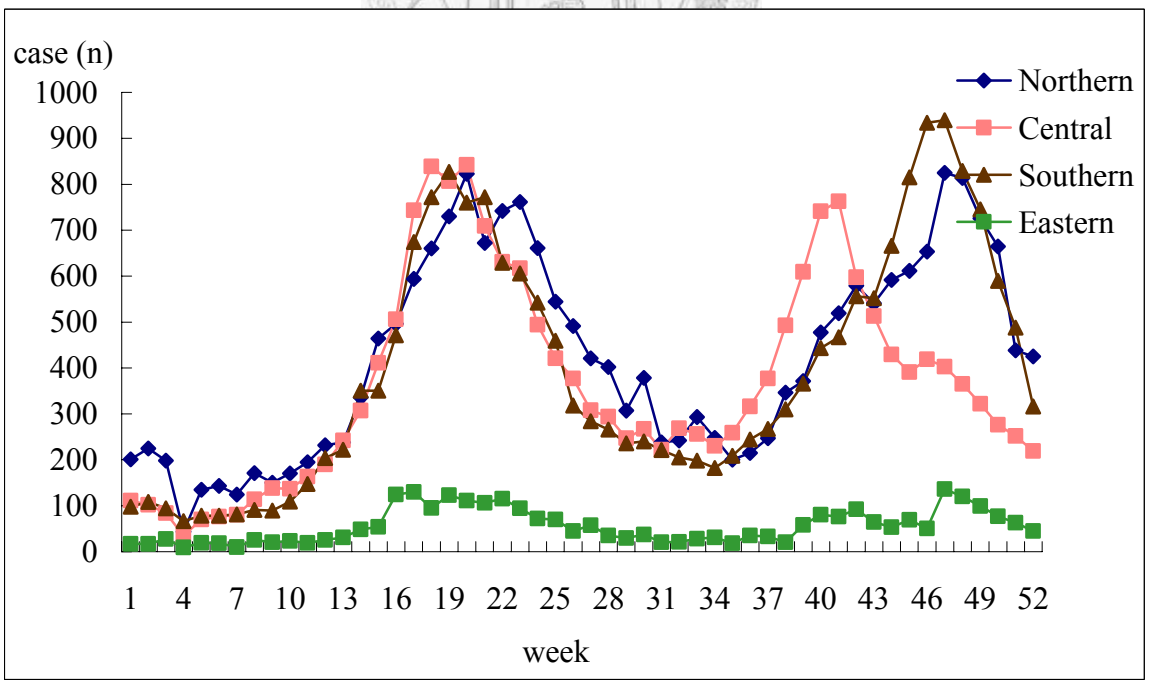

Figure 9- 5 Weekly total cases of HFMD and herpangina by region reported by sentinel physicians at clinics in 2004, Taiwan

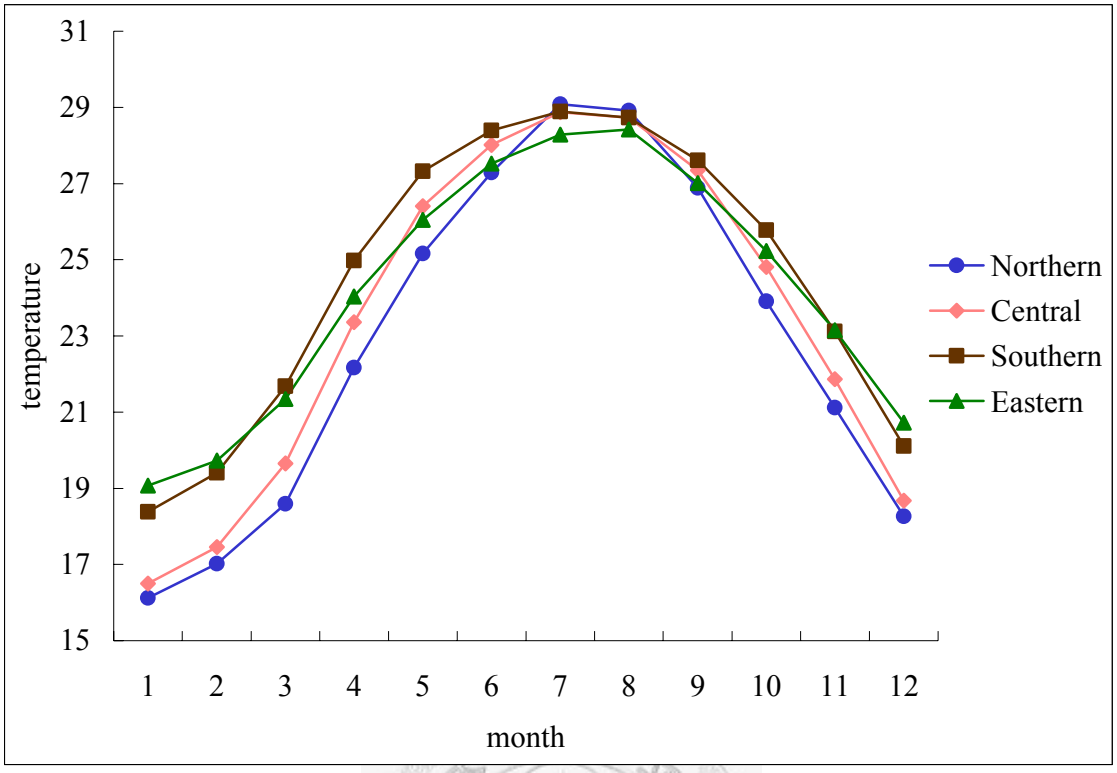

Figure 10 Average monthly temperature by region in 2000-2004, Taiwan

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Appendix 1

Population information

Table 1 Annual population size of children younger than 10 years of age by region, 2000-2004, Taiwan

Region	2000	2001	2002	2003	2004	Total
Northern	1361552	1345498	1317291	1279897	1236697	6540935
Central	721853	712347	697623	677846	654320	3463989
Southern	934866	918643	897026	869446	836120	4456101
Eastern	81556	79584	77749	75214	71935	386038
Total	3099827	3056072	2989689	2902403	2799072	14847063

Table 2 Annual population size of children younger than 10 years old by age, 2000-2004, Taiwan

Age	2000	2001	2002	2003	2004	Total
<1 year	279576	267588	239675	225262	210470	1222571
1-	272900	292364	279601	249749	234938	1329552
2-	293526	273439	292674	279793	249922	1389354
3-	321143	293710	273428	292533	279550	1460364
4-	321787	321307	293712	273380	292470	1502656
5-9	1610895	1607664	1610599	1581686	1531722	7942566
Total	3099827	3056072	2989689	2902403	2799072	14847063

Table 3- 1 Population of boys younger than 10 years old by age and year, 2000-2004, Taiwan

Age	2000	2001	2002	2003	2004	Total
<1 year	146077	139655	125133	117988	110427	639280
1-	142333	152684	145775	130289	122935	694016
2-	152914	142573	152817	145848	130372	724524
3-	167324	153006	142564	152735	145728	761357
4-	167280	167387	153018	142554	152684	782923
5-9	840422	837345	837952	822780	797208	4135707
Total	1616350	1592650	1557259	1512194	1459354	7737807

Table 3- 2 Population of girls younger than 10 years old by age and year, 2000-2004, Taiwan

Age	2000	2001	2002	2003	2004	Total
<1 year	133499	127933	114542	107274	100043	583291
1-	130567	139680	133826	119460	112003	635536
2-	140612	130866	139857	133945	119550	664830
3-	153819	140704	130864	139798	133822	699007
4-	154507	153920	140694	130826	139786	719733
5-9	770473	770319	772647	758906	734514	3806859
Total	1483477	1463422	1432430	1390209	1339718	7109256

Table 4 Population size by age and gender in 2000-2004, Taiwan

Age	Boys	Girls	Total
<1 year	639280	583291	1222571
1-	694016	635536	1329552
2-	724524	664830	1389354
3-	761357	699007	1460364
4-	782923	719733	1502656
5-9	4135707	3806859	7942566
Total	7737807	7109256	14847063

Table 5 Annual population size by gender in 2000-2004 in Taiwan

Year	Boys	Girls	Total
2000	1616350	1483477	3099827
2001	1592650	1463422	3056072
2002	1557259	1432430	2989689
2003	1512194	1390209	2902403
2004	1459354	1339718	2799072
Total	7737807	7109256	14847063

Table 6 Population density in the countries of Taiwan, 2000-2004

Taiwan	Population Density/km^2				category	Population density	category
	2000	2001	2002	2003		2004	
North Taiwan							
Taipei Municipality	9736.9	9690.2	9719.9	9665.7	1	9648.6	1
Taipei County	1738.3	1758.9	1774.1	1791.2	1	1806.6	1
Keelung City	2925.8	2944.9	2948.6	2954.5	1	2955.3	1
Ilan County	217.0	217.3	216.5	216.1	2	215.7	2
Taoyuan County	1419.1	1443.9	1468.2	1492.3	2	1517.7	1
Hsinchu City	3539.4	3586.1	3638.9	3678.3	1	3717.2	1
Hsinchu County	308.0	312.6	317.1	321.7	2	327.3	2
Middle Taiwan							
Mioali County	307.5	308.0	308.7	308.1	2	308.0	2
Taichung City	5909.7	6019.2	6098.8	6176.4	1	6249.3	1
Taichung County	728.4	732.3	736.9	741.1	2	744.4	2
Chaghwa County	1219.8	1223.0	1225.0	1225.3	2	1225.6	2
Nantou County	131.9	131.9	131.8	131.6	2	131.1	2
South Taiwan							
Yunlin County	575.9	576.0	575.4	573.7	2	570.8	2
Chiayi City	4434.5	4464.7	4463.2	4491.3	1	4503.8	1
Chiayi County	295.7	296.3	295.7	294.7	2	293.4	2
Tainan City	4182.6	4217.9	4242.0	4267.8	1	4298.0	1
Tainan County	549.5	549.3	549.4	549.0	2	548.5	2
Kaohsiung Municipality	9704.6	9730.0	9828.0	9827.0	1	9848.6	1
Kaohsiung County	442.1	442.9	441.7	443.1	2	443.6	2
Pingtung County	327.0	327.6	326.5	325.6	2	324.3	2
East Taiwan							
Taitung County	69.8	69.6	69.4	69.1	2	68.4	2
Hualien County	76.4	76.3	76.1	75.9	2	75.4	2

Appendix 2

Confirmed severe cases

Table 1 Percentage distribution of confirmed severe cases of enteroviral infection by region in children younger than 10 years of age during 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	case	%	case	%	case	%	case	%	case	%
Northern	85	30.0	122	31.4	39	24.5	10	14.7	12	24.0
Central	54	19.1	88	22.7	45	28.3	39	57.4	23	46.0
Southern	138	48.8	166	42.8	69	43.4	19	27.9	15	30.0
Eastern	6	2.1	12	3.10	6	3.8	0	0	0	0
Total	283	100	388	100	159	100	68	100	50	100

Table 2 Percentage distribution of confirmed enteroviral severe cases by age in children younger than 10 years old during 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	case	%	case	%	case	%	case	%	case	%
<1 year	70	24.7	79	20.4	30	18.9	12	17.6	7	14.0
1-	74	26.1	131	33.8	53	33.3	22	32.4	18	36.0
2-	62	21.9	85	21.9	34	21.4	17	25.0	11	22.0
3-	39	13.8	36	9.28	17	10.7	6	8.82	10	20.0
4-	29	10.2	28	7.22	9	5.66	5	7.35	3	6.00
5-9	9	3.18	29	7.47	16	10.1	6	8.82	1	2.00
Total	283	100	388	100	159	100	68	100	50	100

Table 3 Annual case number and incidence rates of confirmed severe cases of enteroviral infection by region, 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
Region	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate
Northern	85	6.24	122	9.07	39	2.96	10	0.78	12	0.97
Central	54	7.48	88	12.4	45	6.45	39	5.75	23	3.52
Southern	138	14.8	166	18.1	69	7.69	19	2.19	15	1.79
Eastern	6	7.36	12	15.1	6	7.72	0	0	0	0

Incidence rate=(cases/population size)*100000

Table 4 Annual case number and incidence rates of confirmed severe cases of enteroviral infection by age, 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate
<1year	70	25.0	79	29.5	30	12.5	12	5.33	7	3.33
1-	74	27.1	131	44.8	53	19.0	22	8.81	18	7.66
2-	62	21.1	85	31.1	34	11.6	17	6.08	11	4.40
3-	39	12.1	36	12.3	17	6.22	6	2.05	10	3.58
4-	29	9.01	28	8.71	9	3.06	5	1.83	3	1.03
5-9	9	0.56	29	1.80	16	0.99	6	0.38	1	0.07

Incidence rate=(cases/population size)*100000

Table 5 Annual incidence rates of confirmed enteroviral severe case by year and gender in 2000-2004 in Taiwan

	Boys		Girls		Total	
year	case(n)	incidence rate	case(n)	incidence rate	case(n)	incidence rate
2000	182	11.3	115	7.75	297	9.58
2001	231	14.5	158	10.8	389	12.7
2002	104	6.68	68	4.75	172	5.75
2003	43	2.84	27	1.94	70	2.41
2004	30	2.06	20	1.49	50	1.79

Table 6 Multivariates Poisson regression analysis for factors associated with confirmed enteroviral infection of severe cases

Variables	RR	95%CI	P value
Gender			
Boys	1.43	1.26-1.63	<0.0001
Girls	1.00		
Age			
<1 year	20.9	15.7-27.8	<0.0001
1-	28.9	22.0-38.1	<0.0001
2-	19.4	14.6-25.8	<0.0001
3-	9.57	6.99-13.1	<0.0001
4-	6.39	4.55-8.96	<0.0001
5-9	1.00		
Region			
Northern	1.00		
Central	1.70	1.43-2.03	<0.0001
Southern	2.06	1.75-2.42	<0.0001
Eastern	1.38	0.91-2.11	0.1292
Month			
1	2.61	1.44-4.71	0.0015
2	1.00		
3	1.65	0.88-3.11	0.1182
4	3.08	1.69-5.64	0.0003
5	4.75	2.59-8.71	<0.0001
6	5.16	2.79-9.53	<0.0001
7	3.52	1.88-6.58	<0.0001
8	3.40	1.82-6.35	0.0001
9	3.42	1.83-6.39	0.0001
10	4.96	2.74-8.98	<0.0001
11	4.12	2.31-7.37	<0.0001
12	3.08	1.73-5.49	<0.0001
Daily average temperature			
<15℃	1.00		
15-19.9	1.04	0.60-1.79	0.8958
20-24.9	1.18	0.66-2.10	0.5713
25-29.9	1.91	1.02-3.56	0.0432
≧30	1.76	0.84-3.70	0.1371
Daily average sunshine hours			
0-2.49 hrs	1.06	0.86-1.31	0.5805
2.50-4.99	1.00		
5.00-7.49	0.88	0.71-1.09	0.2367
7.50-9.99	0.92	0.75-1.13	0.4178
≧10	0.90	0.69-1.17	0.4296

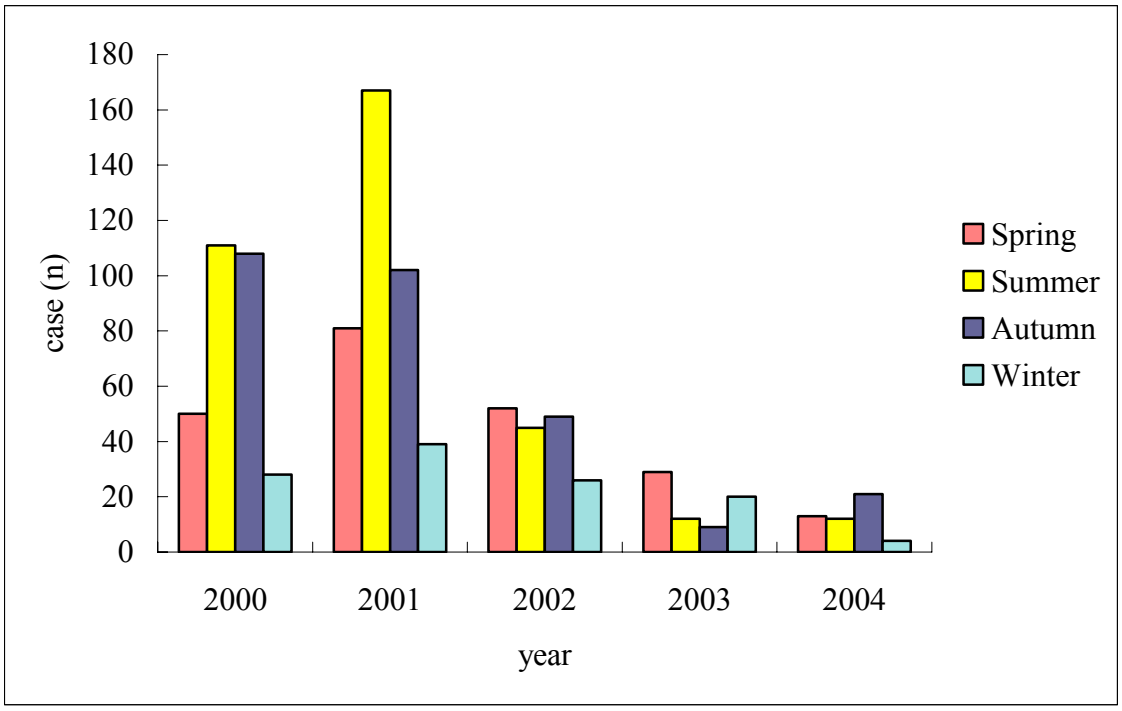


Figure1- 1 Seasonal confirmed cases of enteroviral infection with severe complication by year 2000-2004

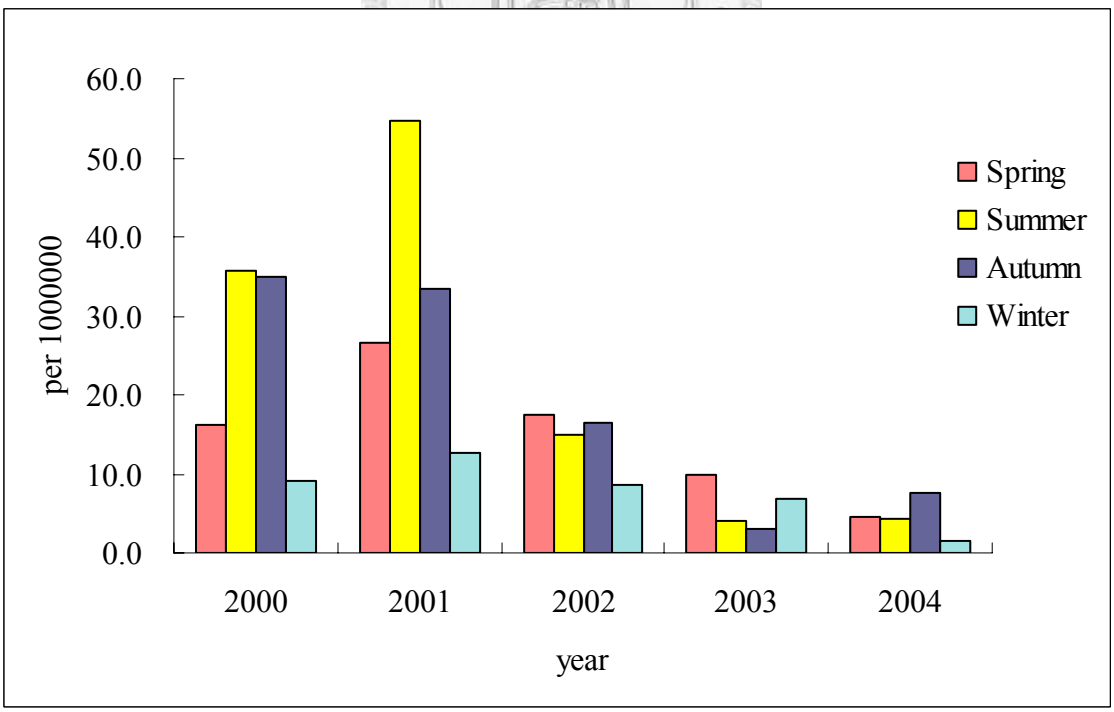


Figure1- 2 Seasonal confirmed incidence rates of enteroviral infection with severe complication by year 2000-2004

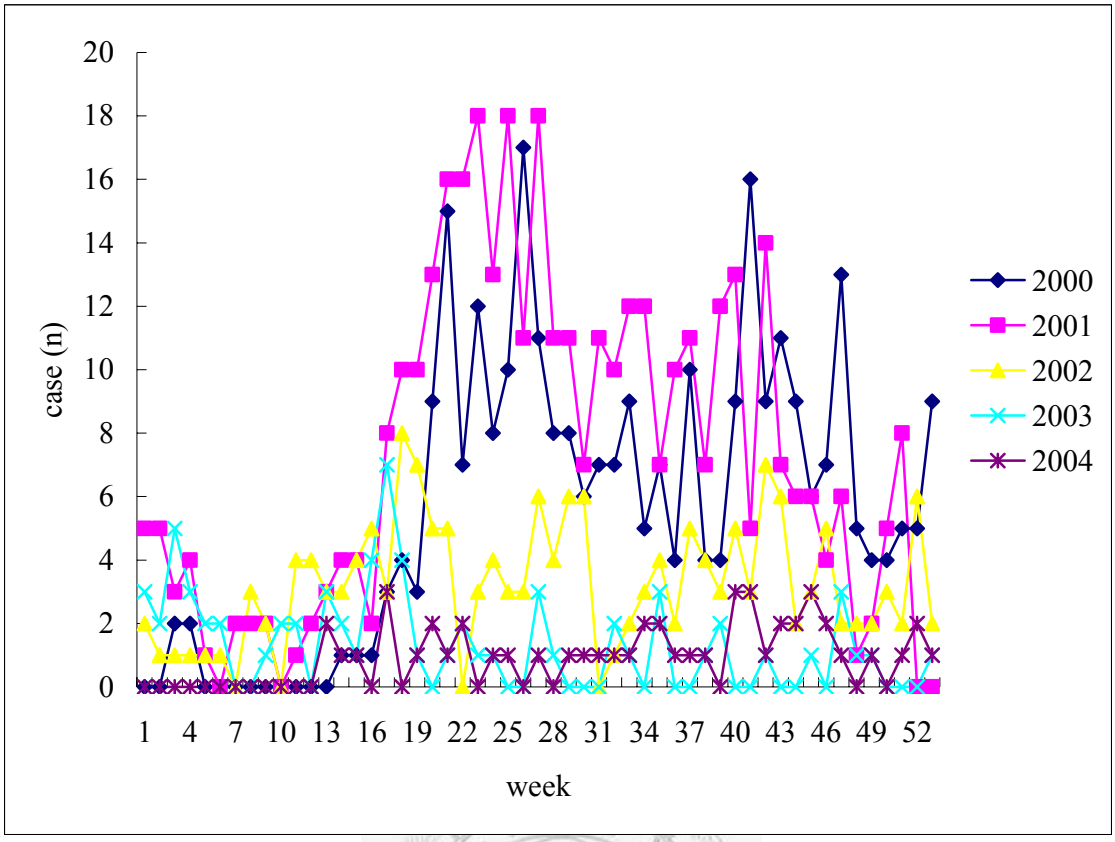


Figure 2 Weekly confirmed cases of enteroviral infection with severe complication by year in 2000-2004 in Taiwan

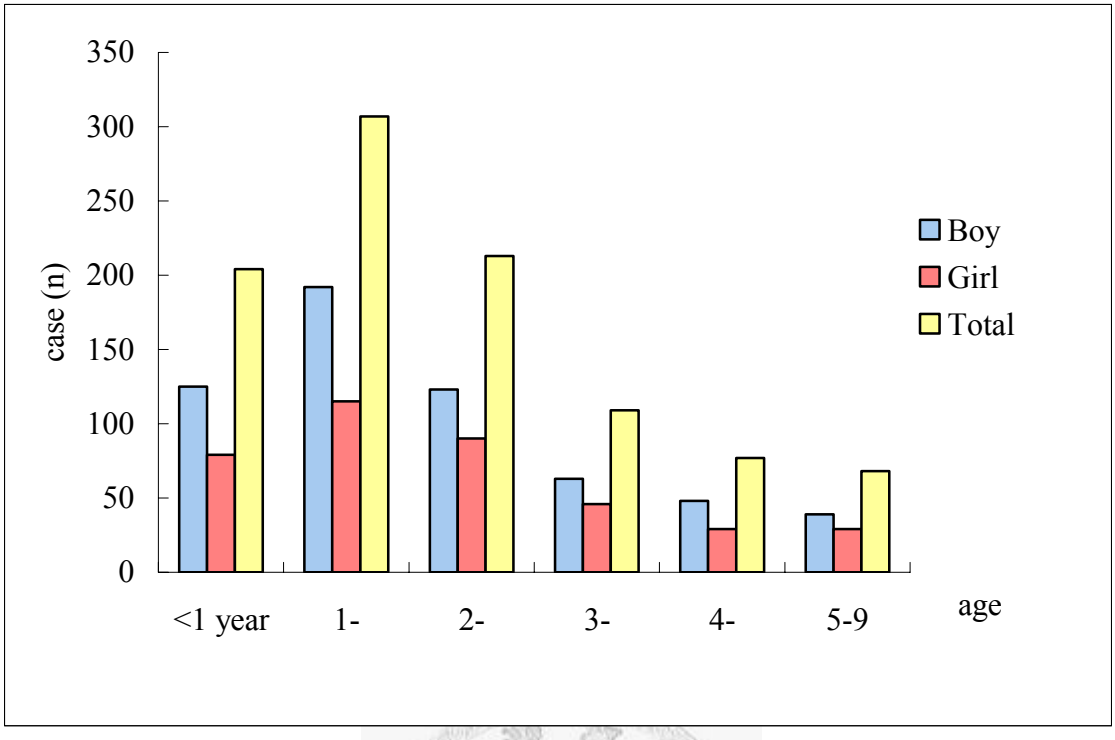


Figure 3- 1 Confirmed severe cases of enteroviral infection by age in children younger than 10 years of age during 2000-2004 in Taiwan

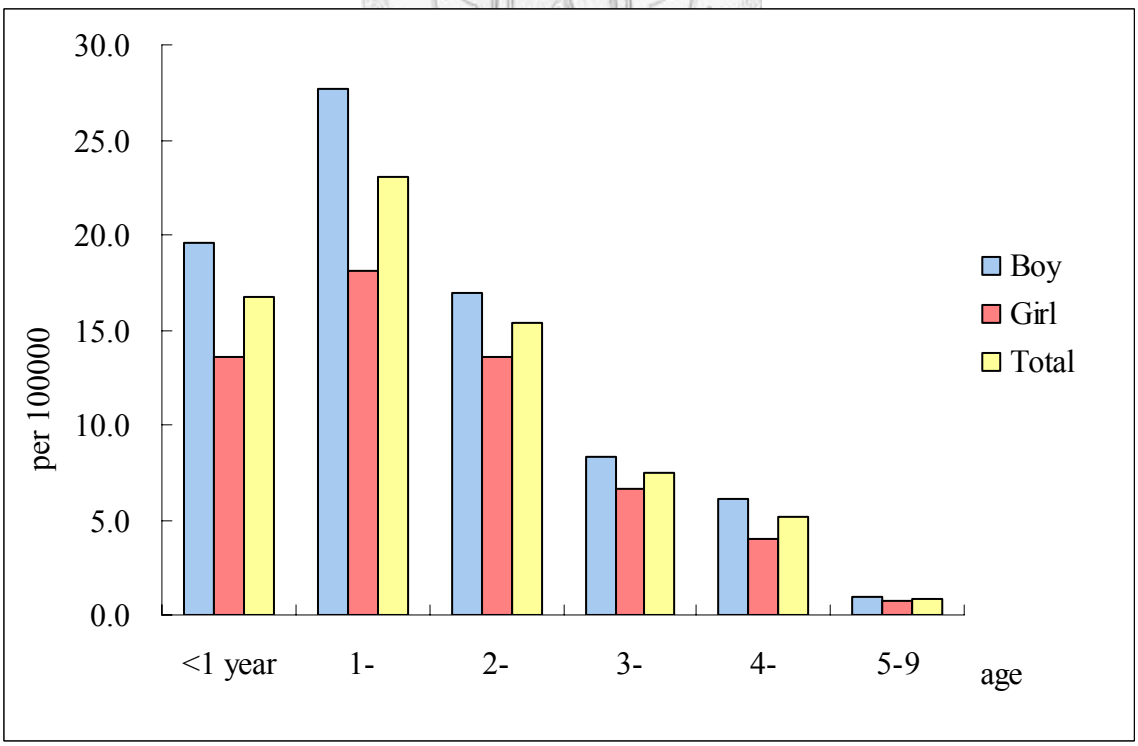


Figure 3- 2 Incidence rates of confirmed enteroviral infection with severe omplication by age in children younger than 10 years of age during 2000-2004 in Taiwan

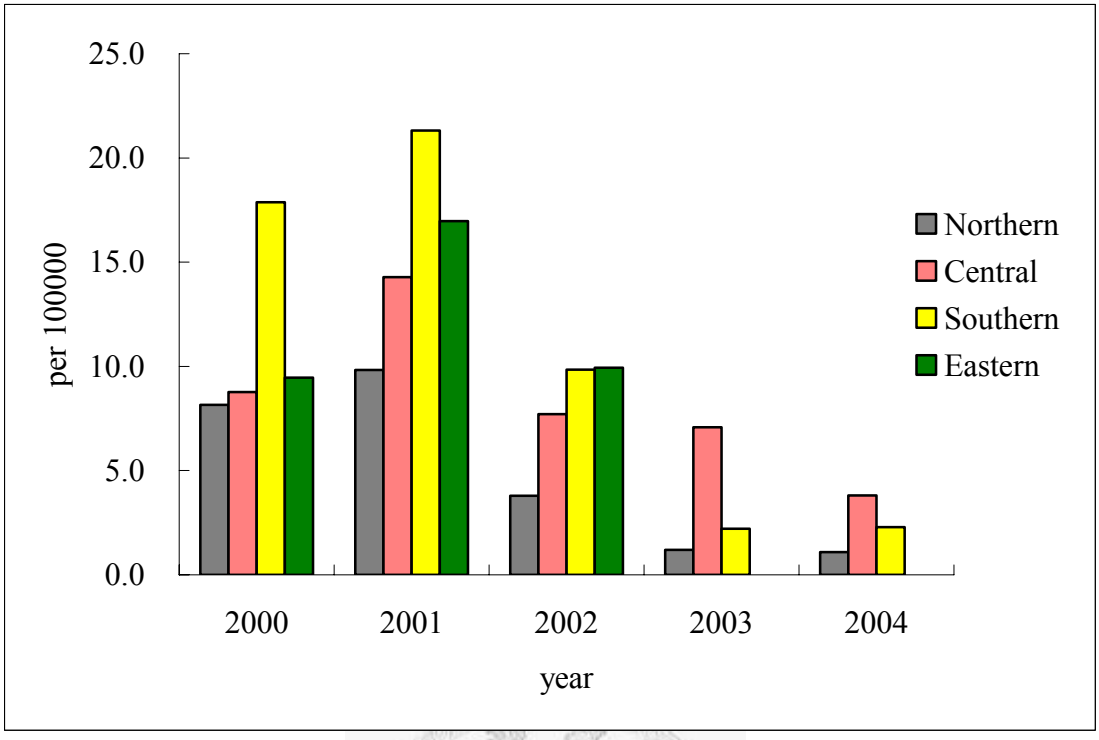


Figure 4- 1 Annual incidence rates of confirmed enteroviral infection with severe complication in boys by region, 2000-2004, Taiwan

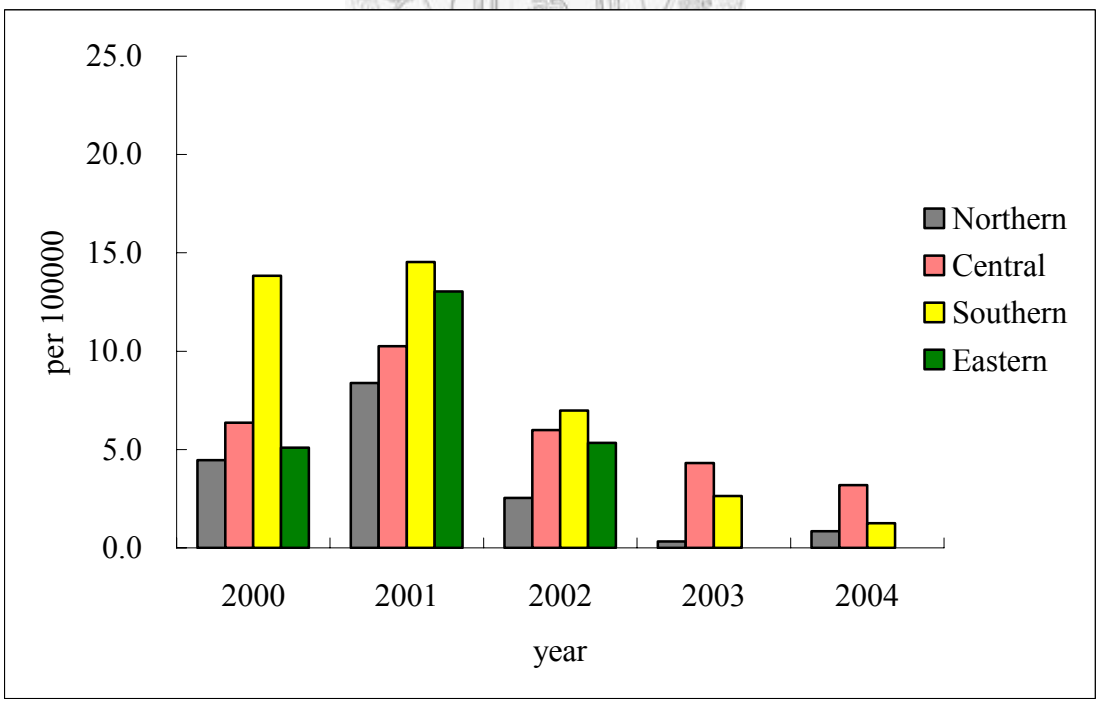


Figure 4- 2 Annual incidence rates of confirmed enteroviral infection with severe complication in girls by region, 2000-2004, Taiwan

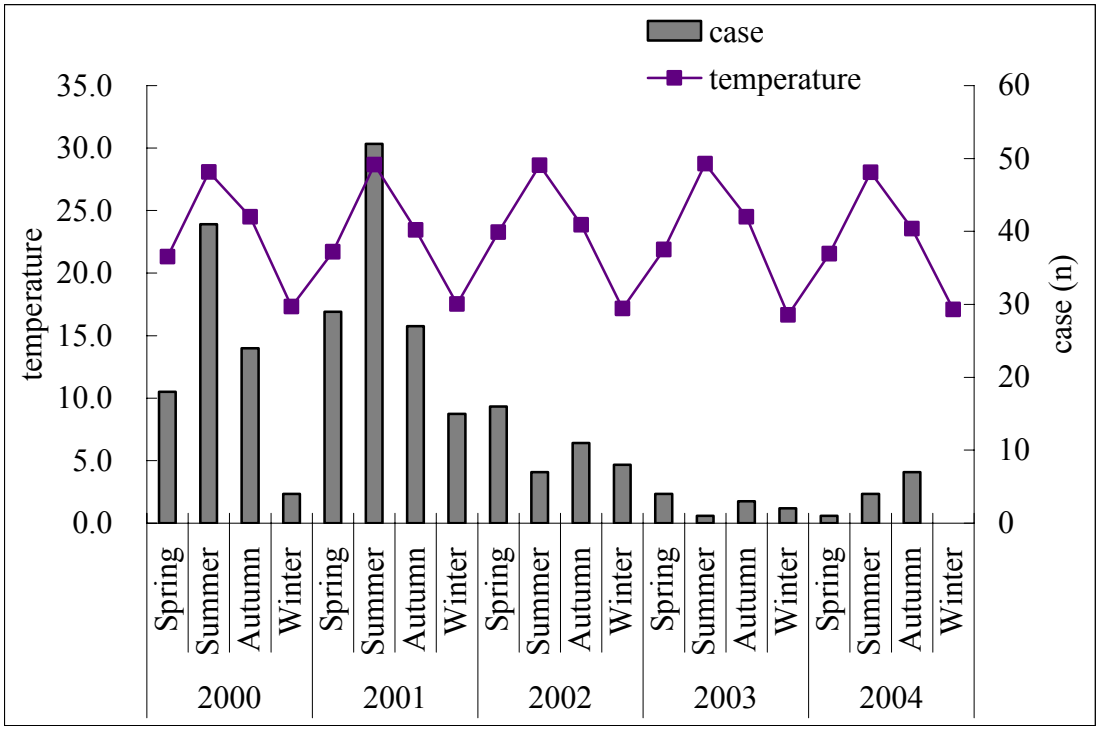


Figure 5- 1 Seasonal average temperature and confirmed enteroviral severe cases in northern region in 2000-2004, Taiwan

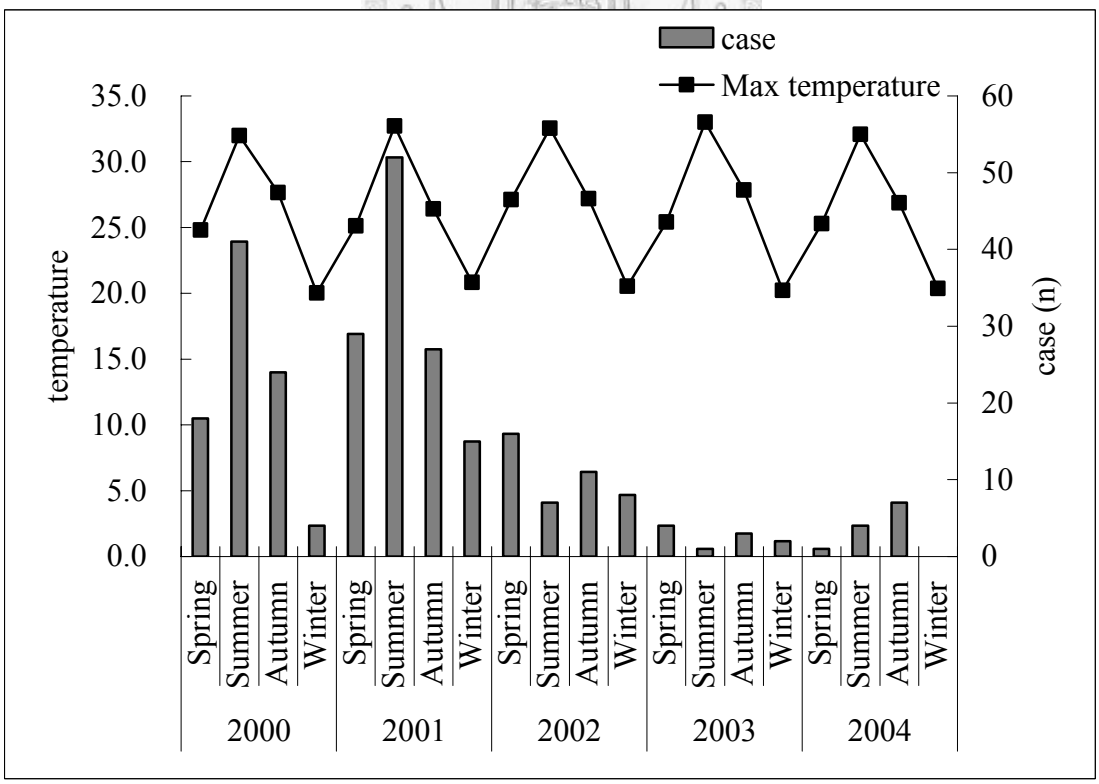


Figure 5- 2 Seasonal average maximum temperature and confirmed enteroviral severe cases in northern region in 2000-2004, Taiwan

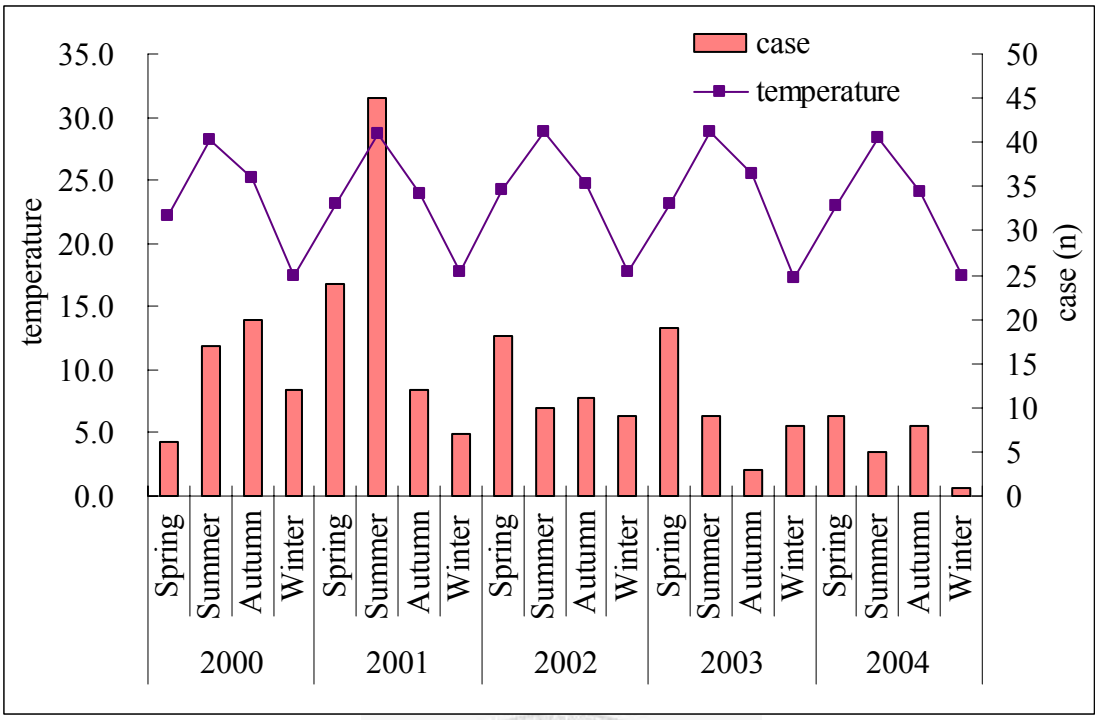


Figure 6- 1 Seasonal average temperature and confirmed enteroviral severe cases in central region in 2000-2004, Taiwan

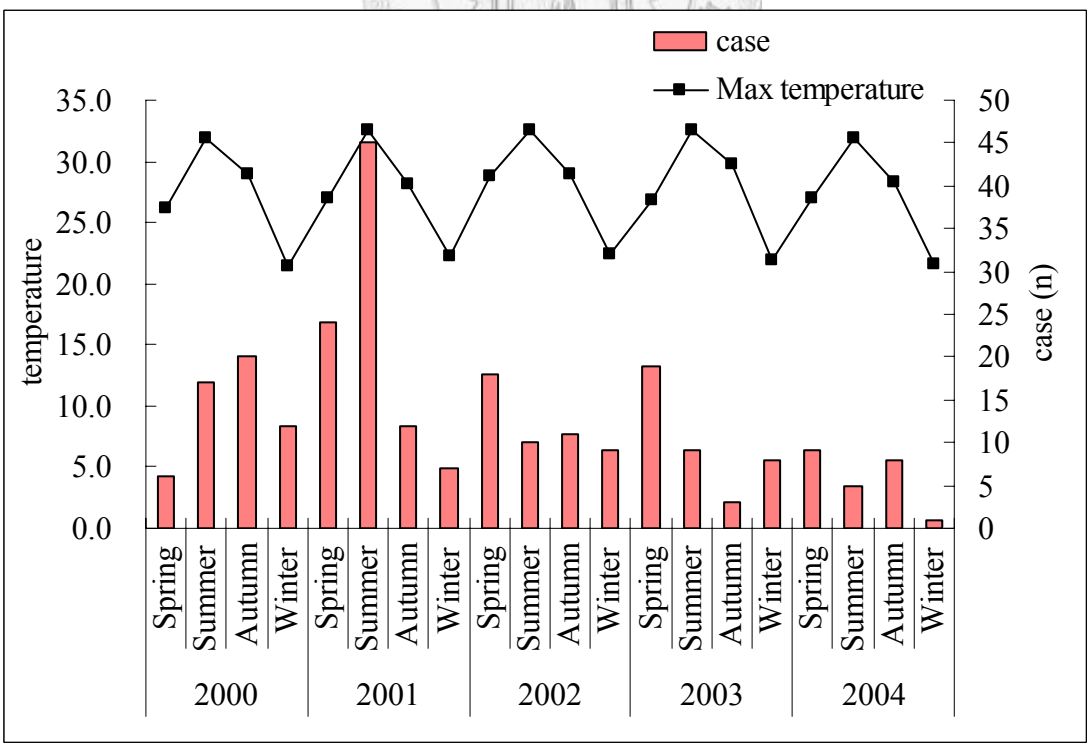


Figure 6- 2 Seasonal average maximum temperature and confirmed enteroviral severe cases in central region in 2000-2004, Taiwan

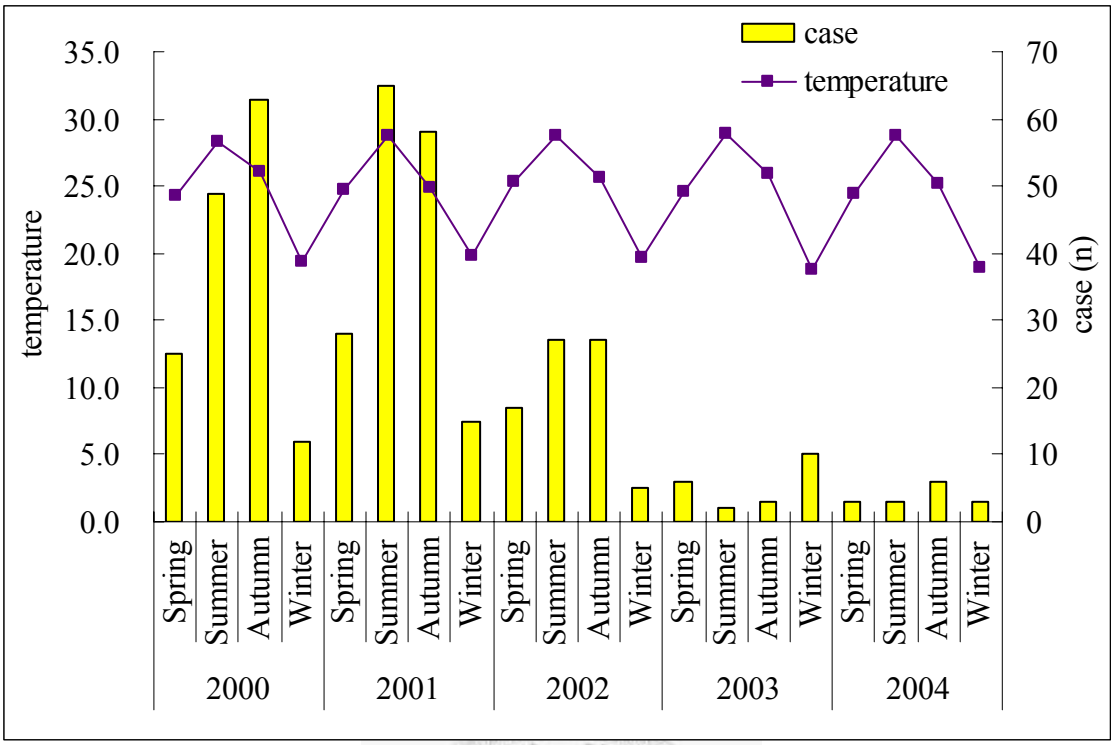


Figure 7- 1 Seasonal average temperature and confirmed enteroviral severe cases in southern region in 2000-2004, Taiwan

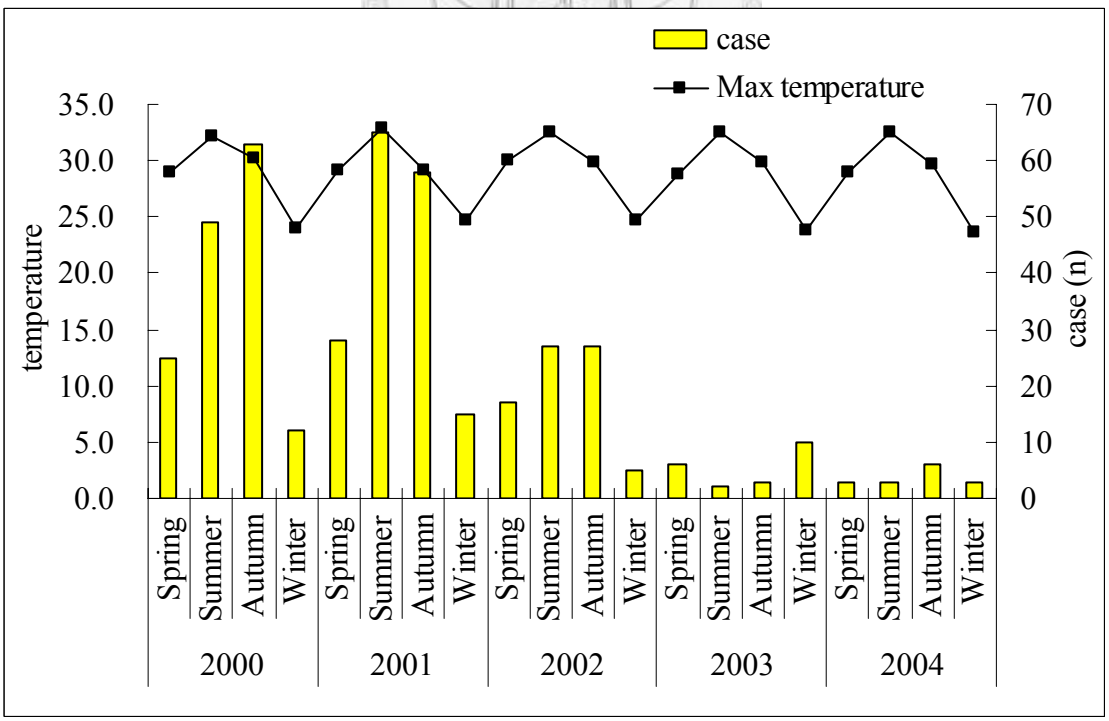


Figure 7- 2 Seasonal average maximum temperature and confirmed enteroviral severe cases in southern region in 2000-2004, Taiwan

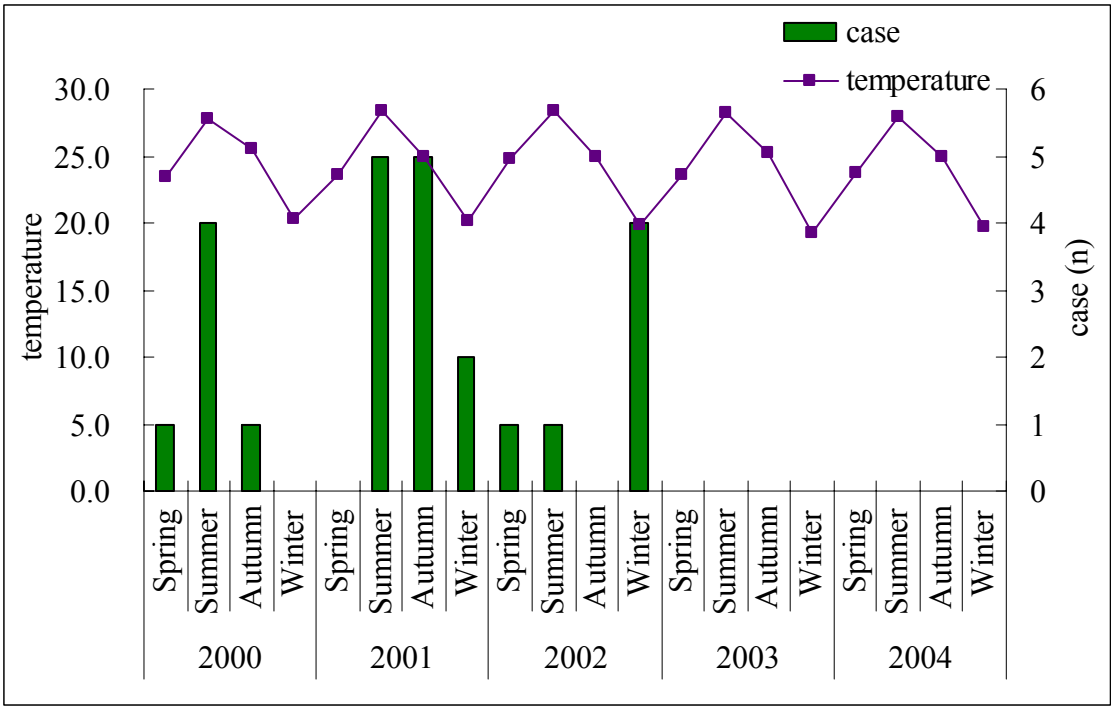


Figure 8- 1 Seasonal average temperature and confirmed enteroviral severe cases in eastern region in 2000-2004, Taiwan

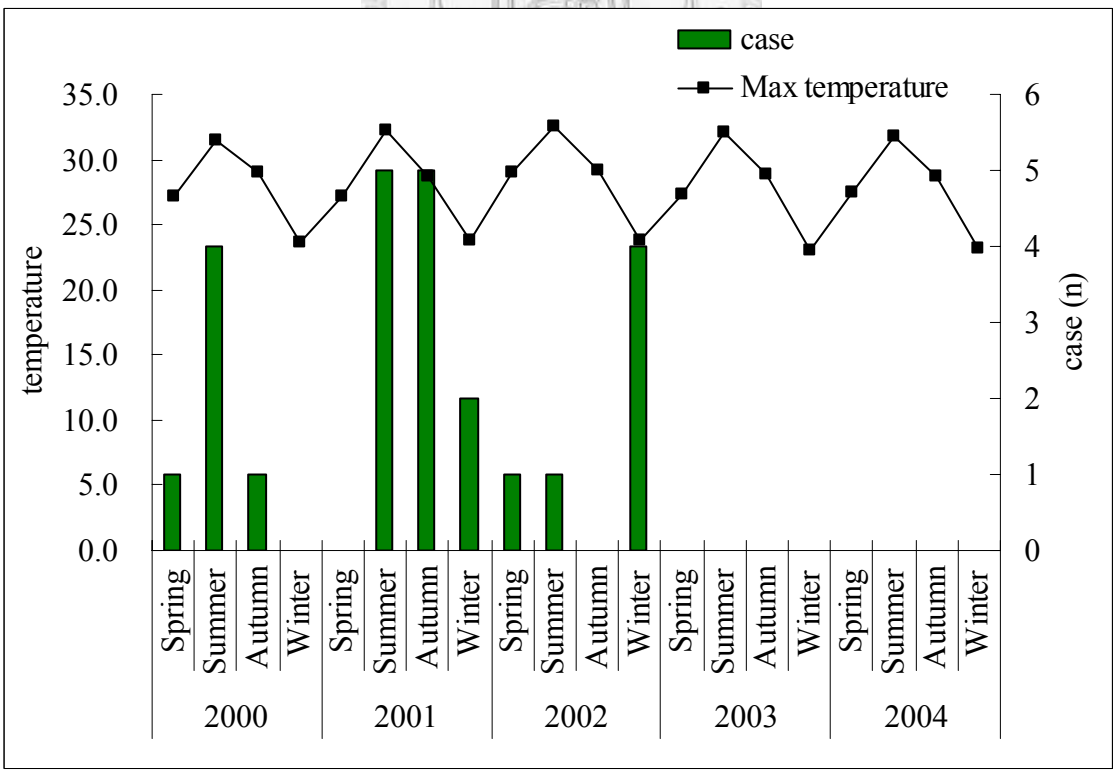


Figure 8- 2 Seasonal average maximum temperature and confirmed enteroviral severe cases in eastern region in 2000-2004, Taiwan

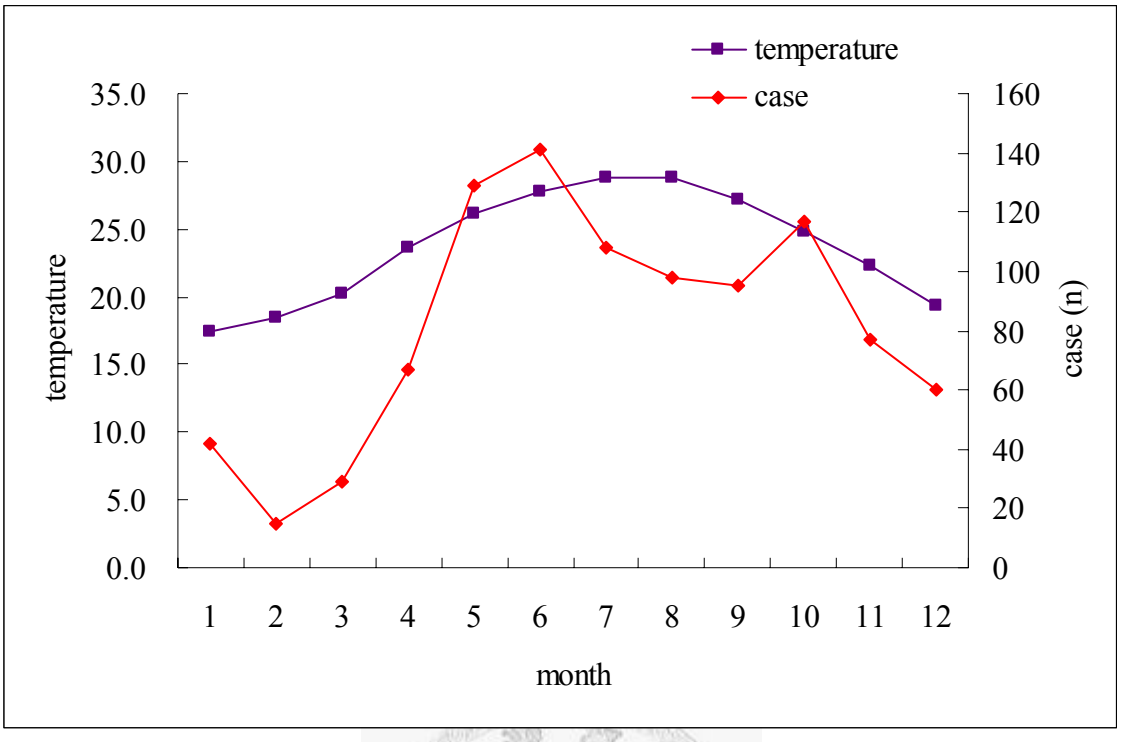


Figure 9-1 Monthly average temperature and confirmed enteroviral severe cases in 2000-2004, Taiwan

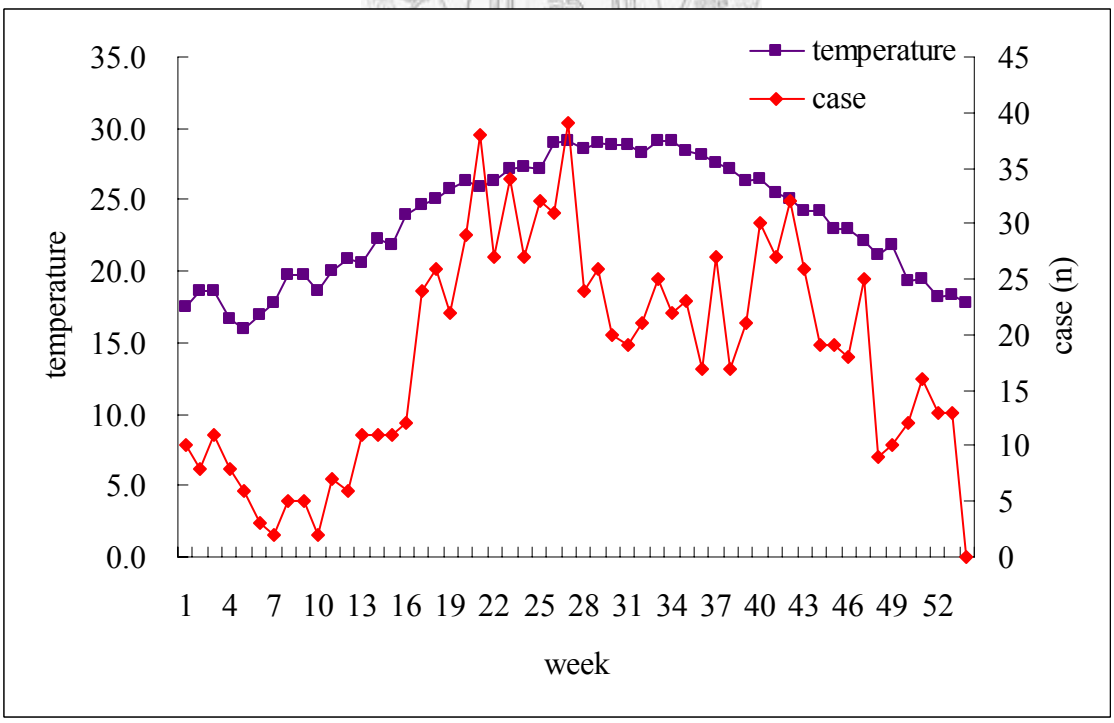


Figure 9- 2 Weekly average temperature and confirmed enteroviral severe cases in 2000-2004, Taiwan

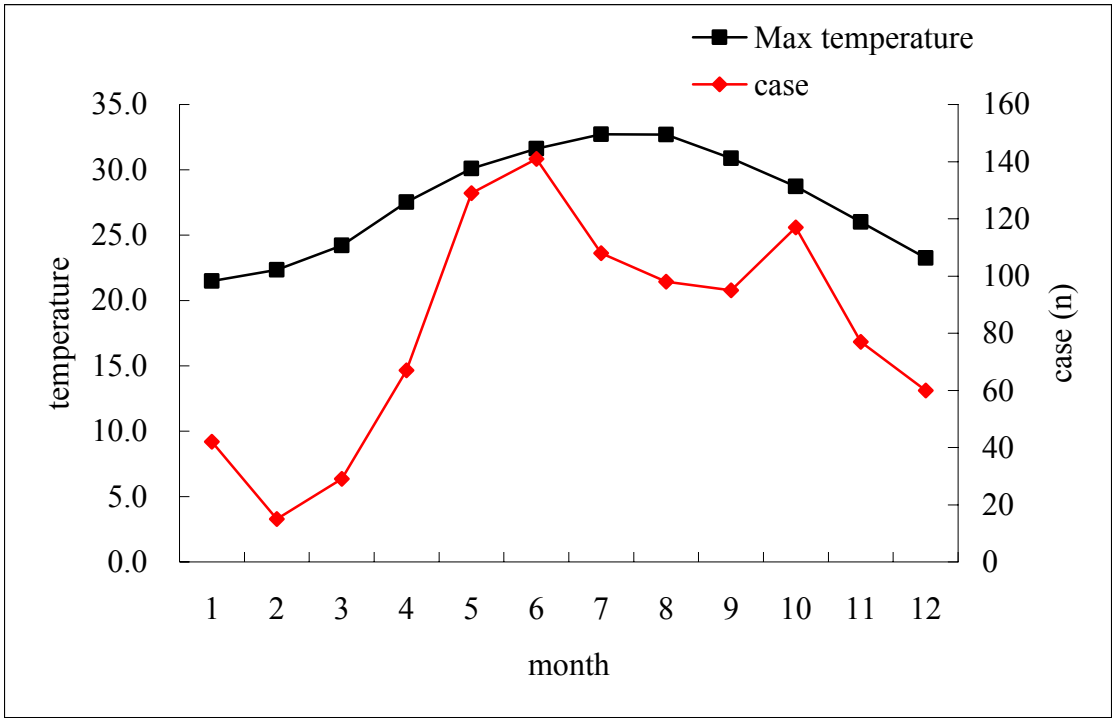


Figure 10-1 Monthly average maximum temperature and confirmed enteroviral severe cases in 2000-2004, Taiwan

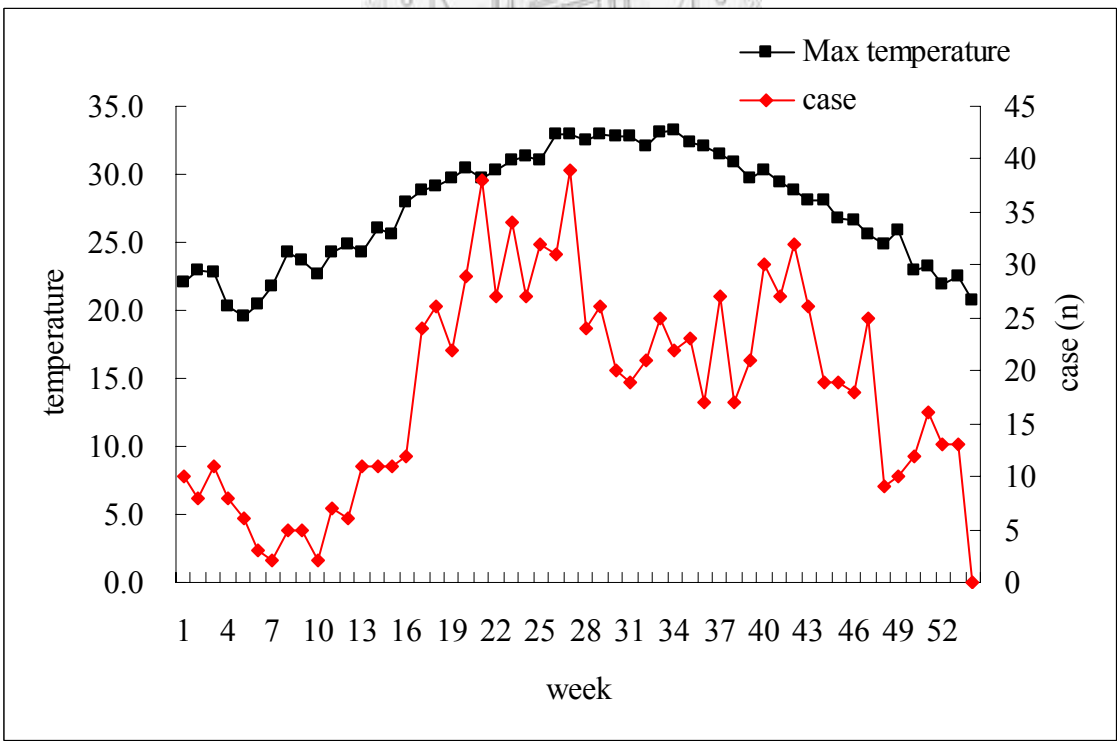


Figure 10- 2 Average highest daily temperature by week and total weekly confirmed enteroviral severe cases in 2000-2004, Taiwan

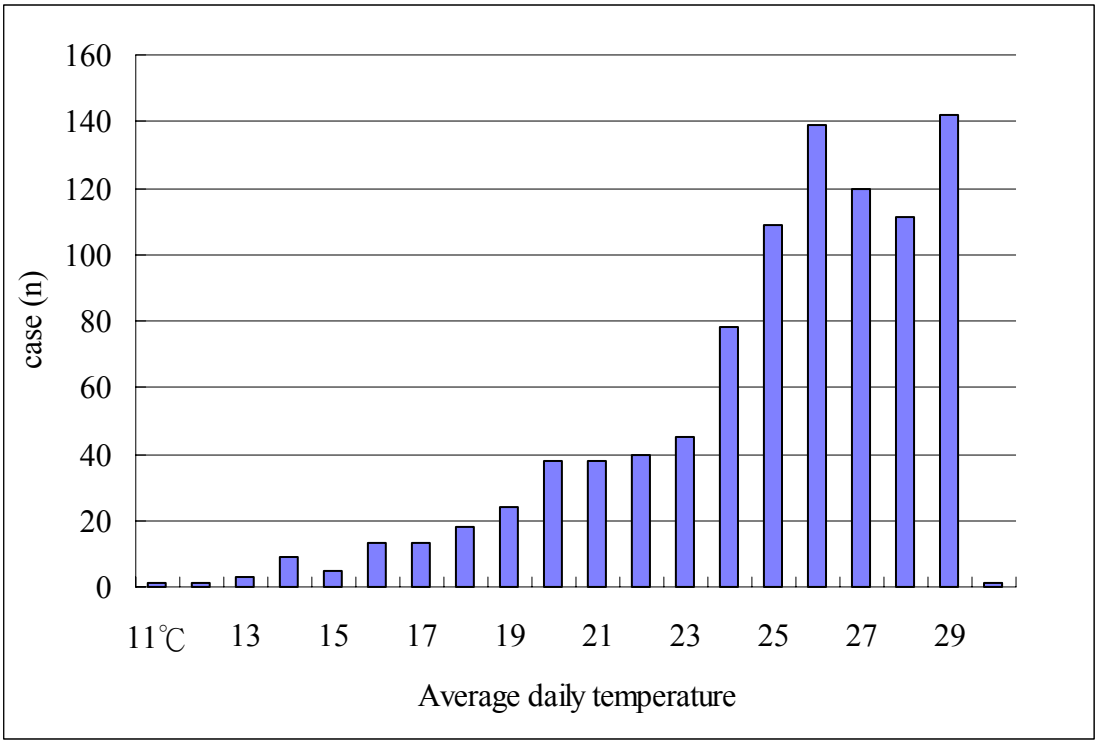


Figure 11-1 Severe cases of enteroviral infection by average daily temperature in Taiwan, 2000-2004

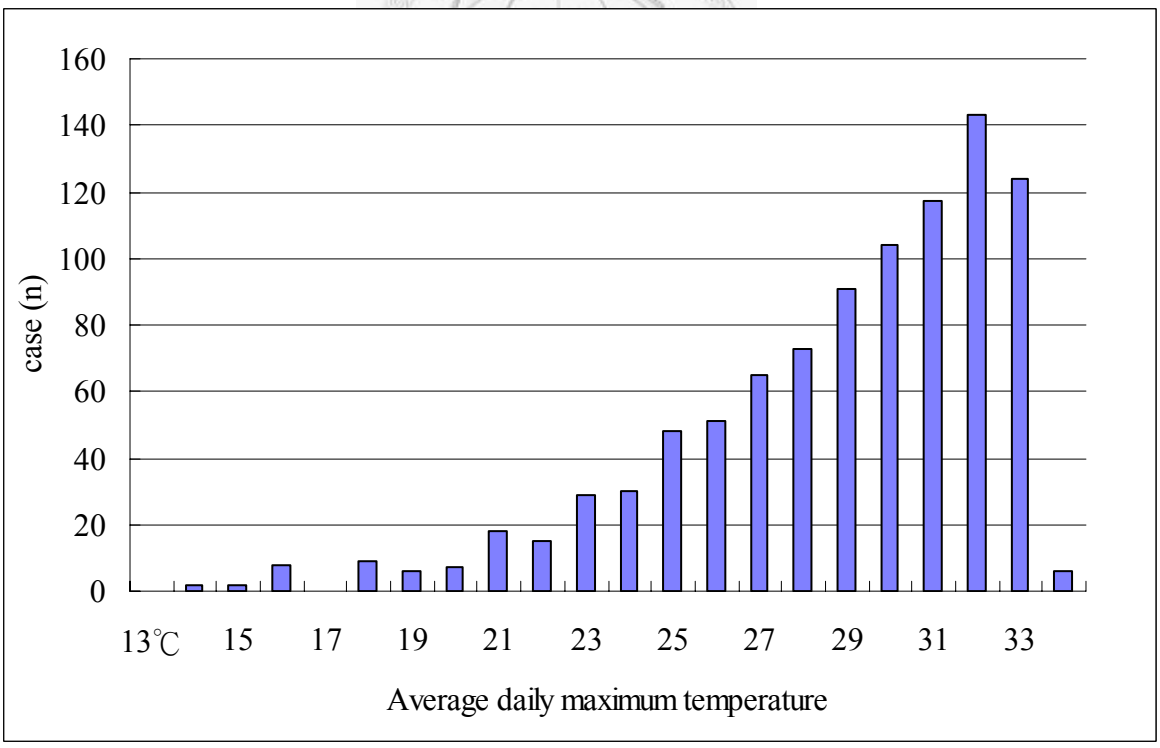


Figure 11-2 Severe cases of enteroviral infection by average daily maximum temperature in Taiwan, 2000-2004

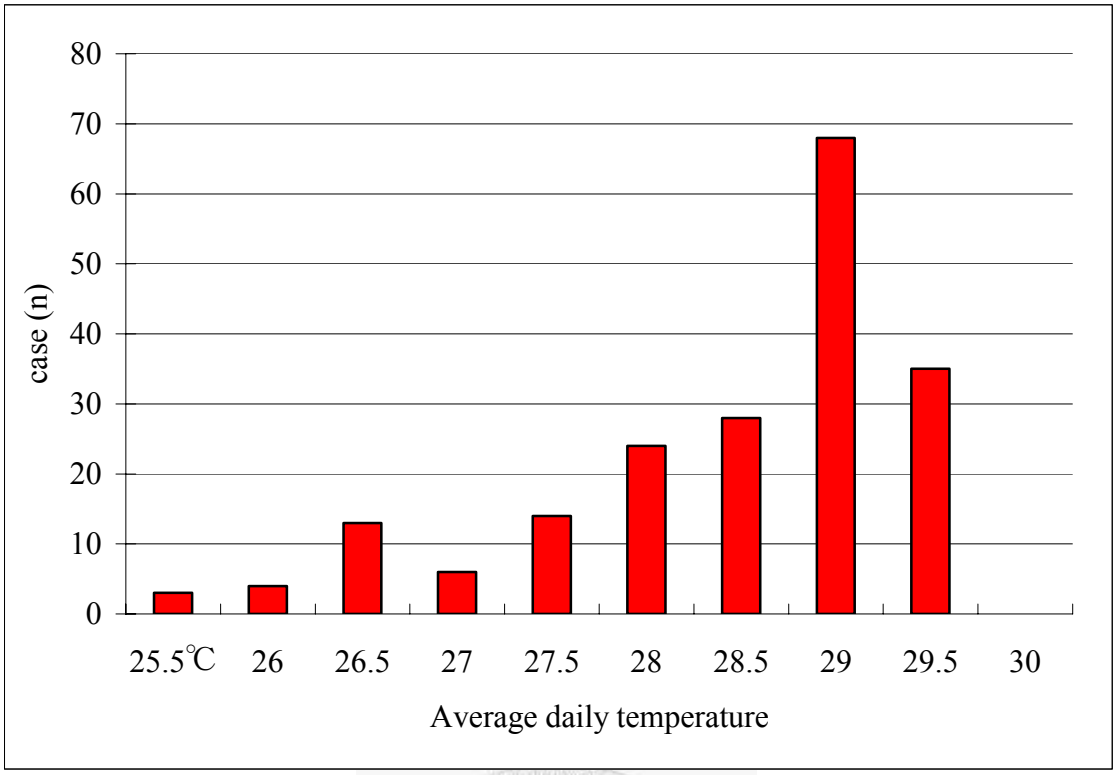


Figure 12-1 Severe cases of enteroviral infection in July and August by average daily temperature in Taiwan, 2000-2004

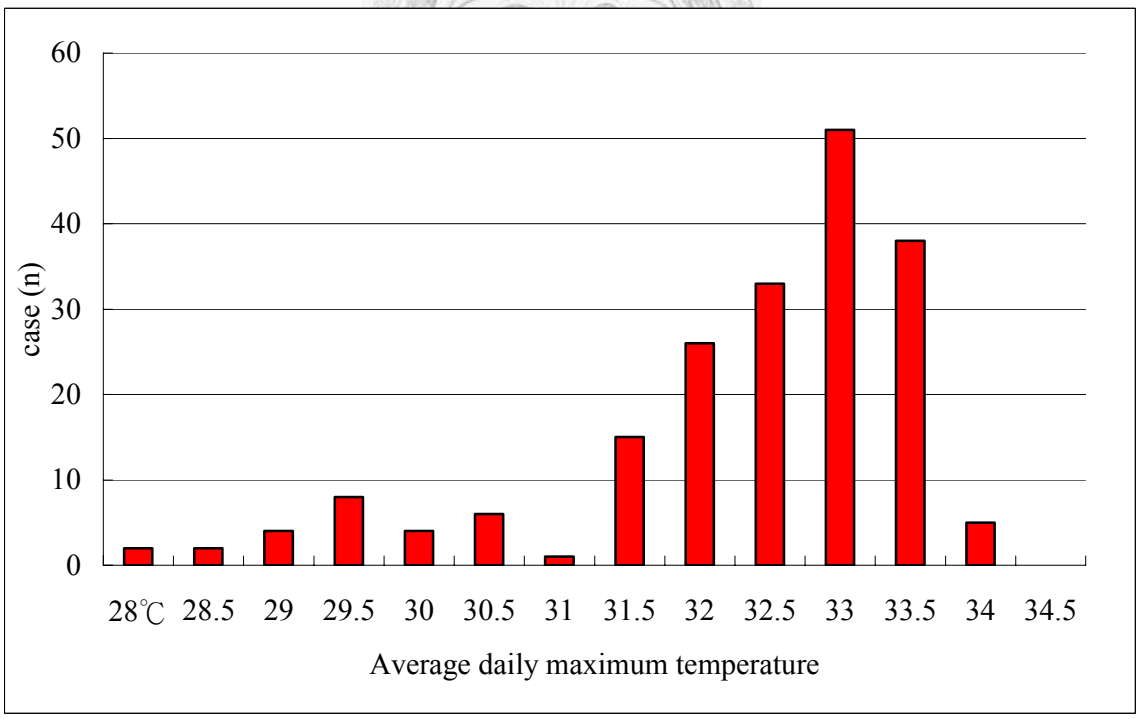


Figure 12-2 Severe cases of enteroviral infection in July and August by average daily maximum temperature in Taiwan, 2000-2004

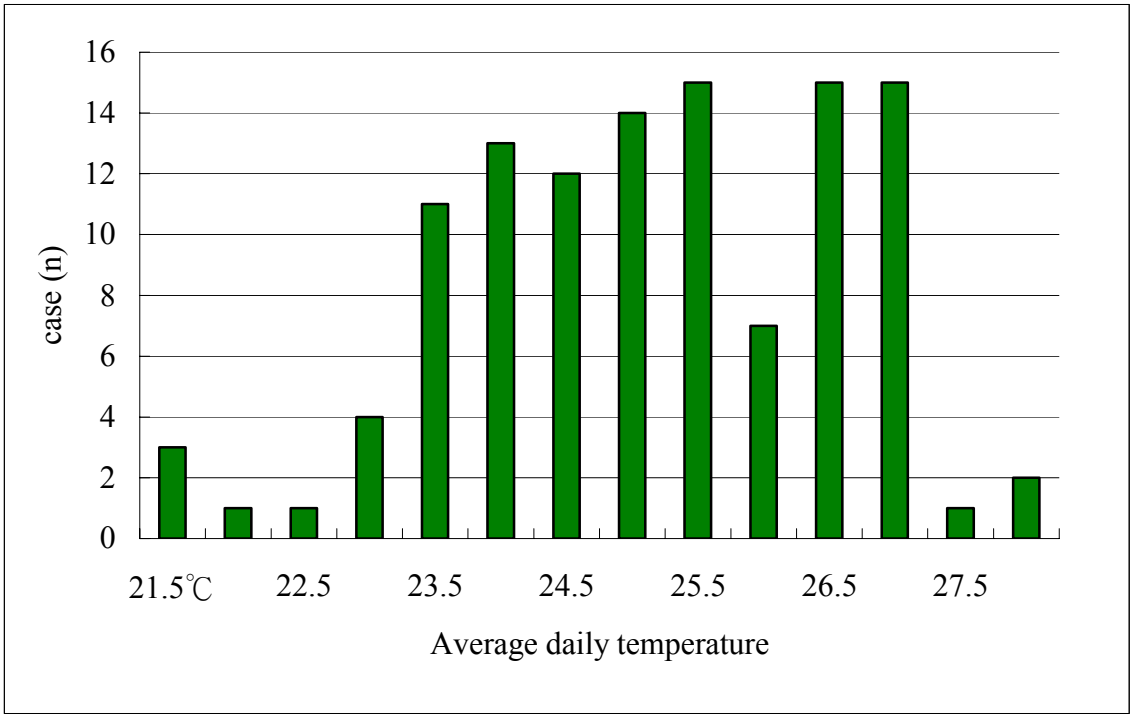


Figure 13-1 Severe cases of enteroviral infection in October by average daily temperature in Taiwan, 2000-2004

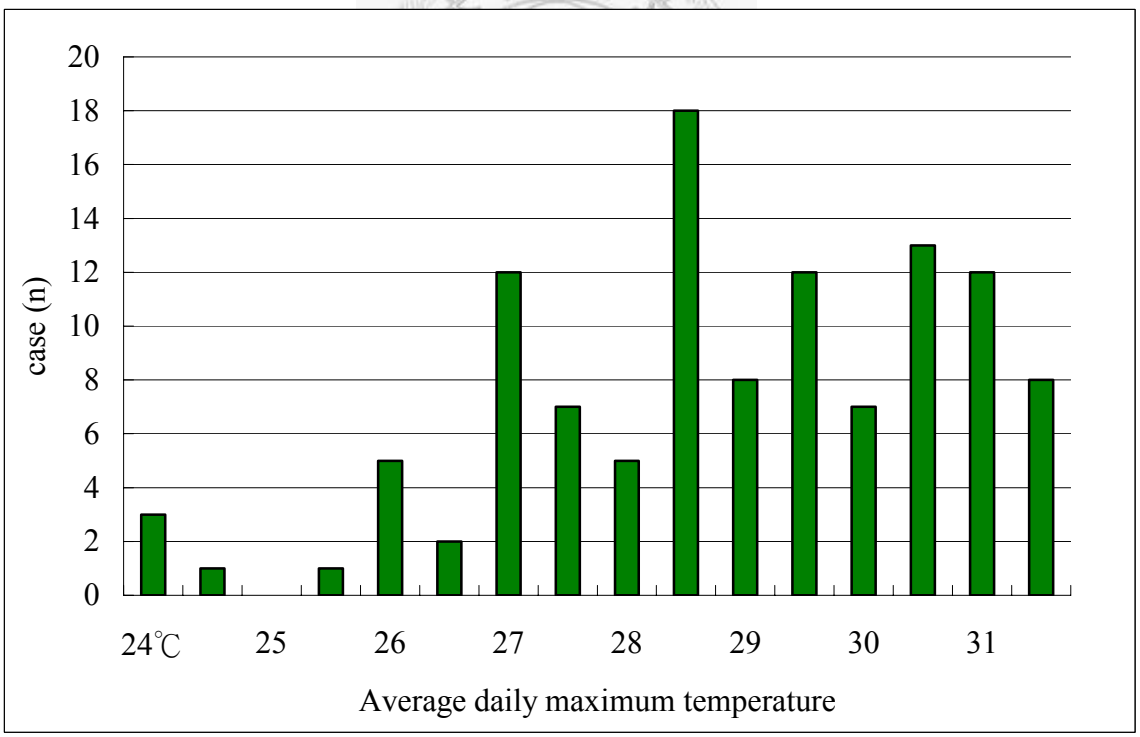


Figure 13-2 Severe cases of enteroviral infection in October by average daily maximum temperature in Taiwan, 2000-2004

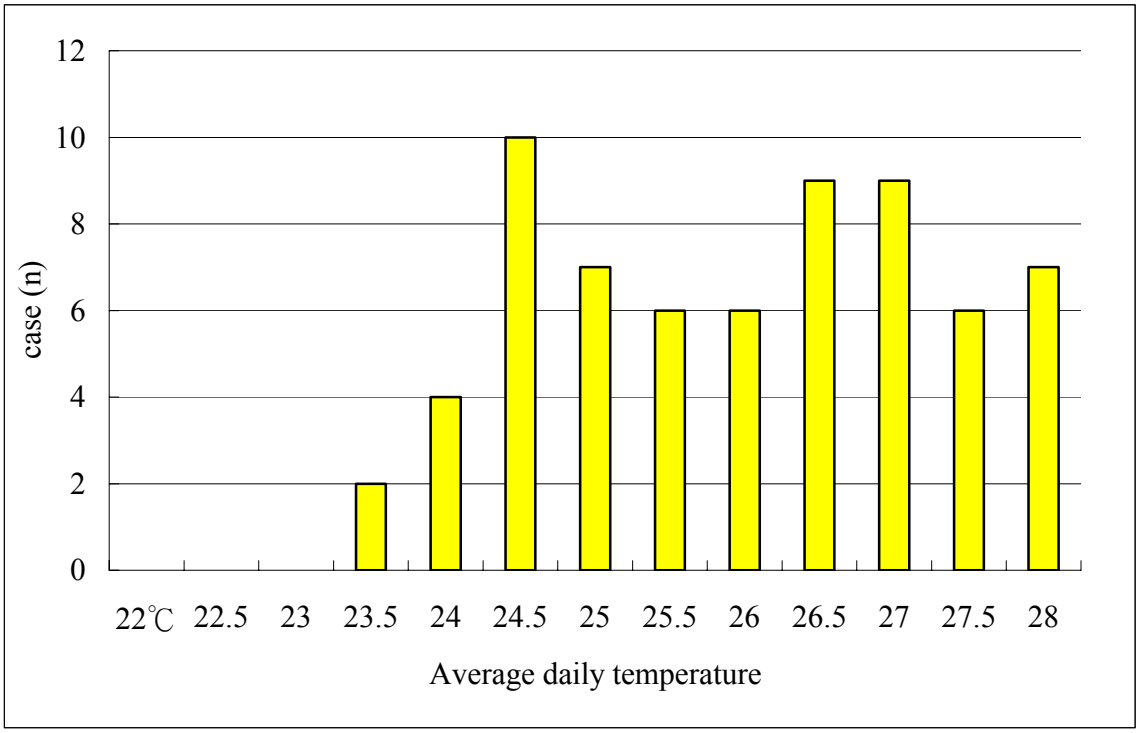


Figure 14-1 Severe cases of enteroviral infection in October by average daily temperature in southern Taiwan, 2000-2004

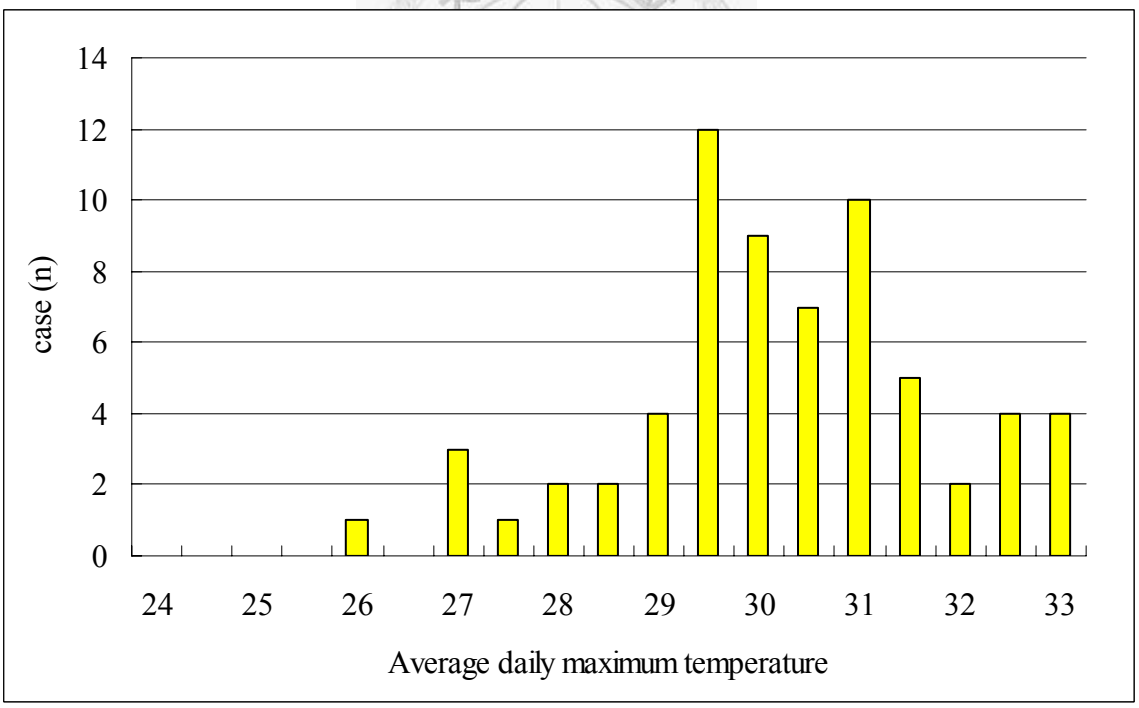


Figure 14-2 Severe cases of enteroviral infection in October by average daily maximum temperature in southern Taiwan, 2000-2004

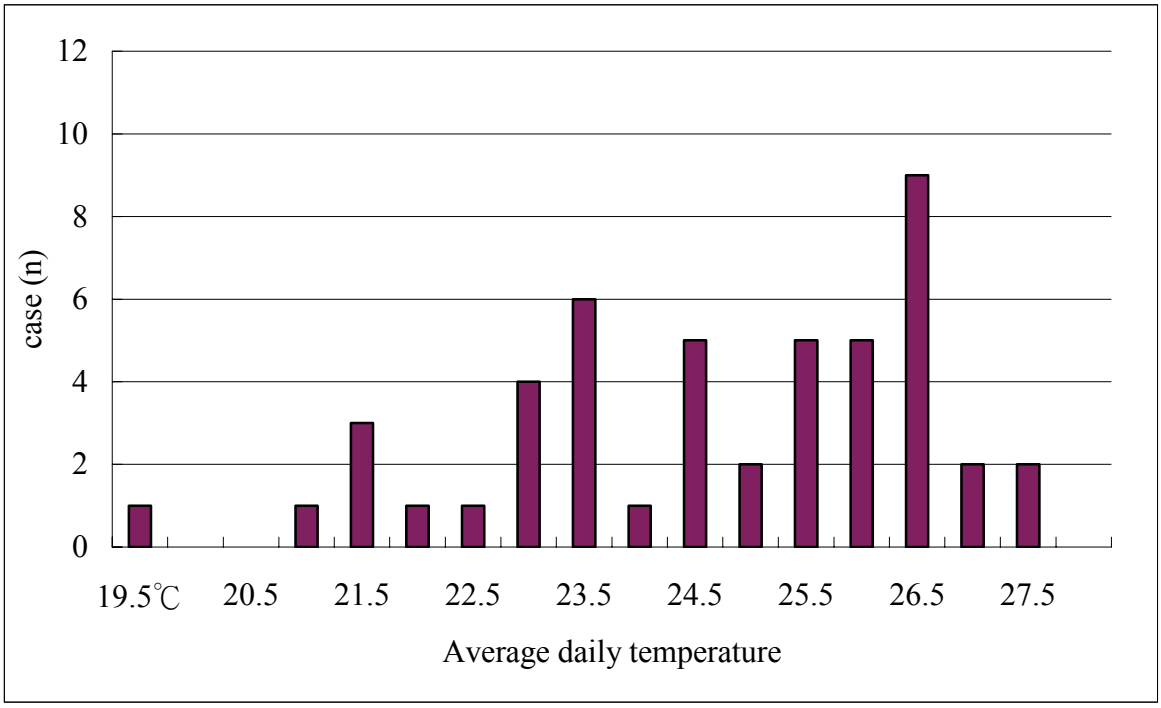


Figure 15-1 Severe cases of enteroviral infection in October by average daily temperature in northern, central and eastern regions of Taiwan, 2000-2004

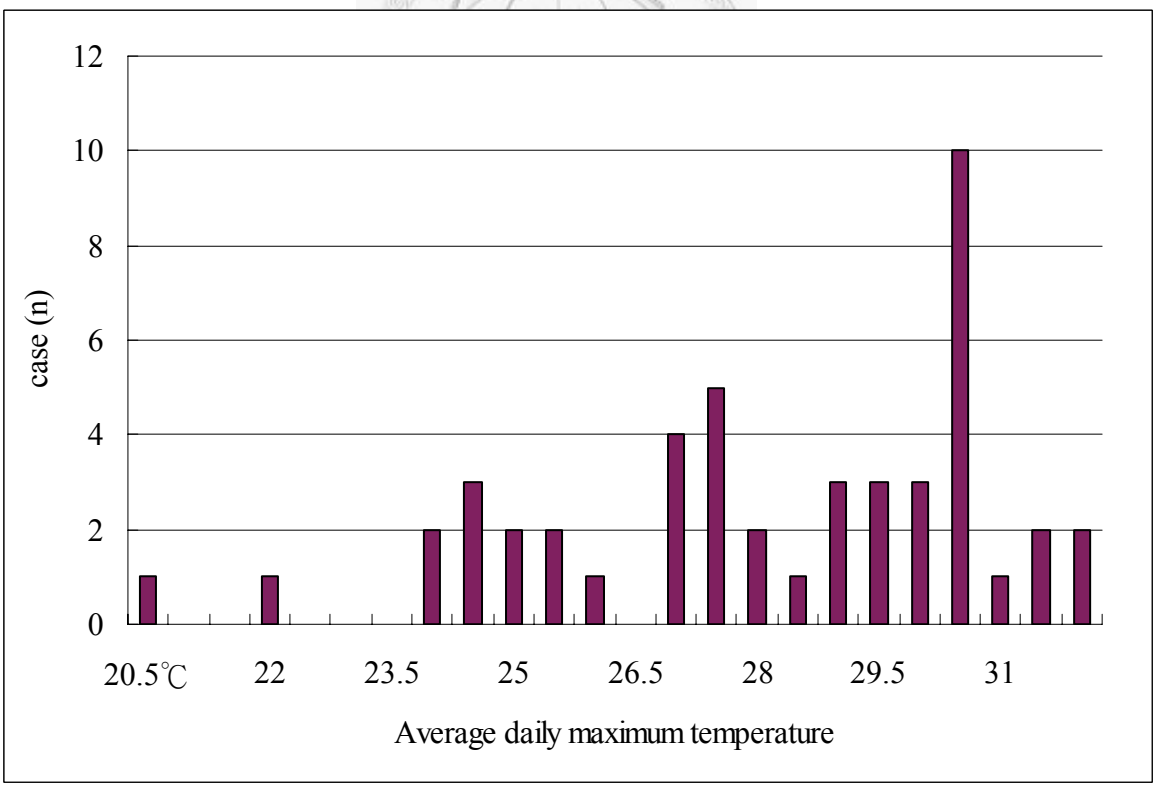


Figure 15-2 Severe cases of enteroviral infection in October by average daily maximum temperature in northern, central and eastern regions of Taiwan, 2000-2004

Appendix 3

Reported severe cases

Table 1 Annual percentage distribution of reported enteroviral severe cases by region in children younger than 10 years of age during 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	case	%	case	%	case	%	case	%	case	%
Northern	115	27.0	167	28.7	83	28.2	22	17.3	37	25.5
Central	74	17.4	133	22.9	69	23.5	55	43.3	38	26.2
Southern	229	53.8	266	45.8	134	45.6	50	39.4	70	48.3
Eastern	8	1.88	15	2.58	8	2.72	0	0	0	0
Total	426	100	581	100	294	100	127	100	145	100

Table 2 Annual percentage distribution of reported enteroviral severe cases by age in children younger than 10 years old during 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	case	%	case	%	case	%	case	%	case	%
<1 year	106	24.9	118	20.3	70	23.8	30	23.6	26	17.9
1-	102	23.9	194	33.4	85	28.9	35	27.6	44	30.3
2-	89	20.9	112	19.3	62	21.1	26	20.5	23	15.9
3-	51	12.0	55	9.47	26	8.84	13	10.2	27	18.6
4-	43	10.1	44	7.57	19	6.46	8	6.30	16	11.0
5-9	35	8.22	58	9.98	32	10.9	15	11.8	9	6.21
Total	426	100	581	100	294	100	127	100	145	100

Table 3 Annual cases and incidence rate of reported enteroviral severe cases by region, 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
Region	n	rate	n	rate	n	rate	n	rate	n	rate
Northern	115	8.45	167	12.4	83	6.30	22	1.72	37	2.99
Central	74	10.3	133	18.7	69	9.89	55	8.11	38	5.81
Southern	229	24.5	266	29.0	134	14.9	50	5.75	70	8.37
Eastern	8	9.81	15	18.9	8	10.3	0	0	0	0

Table 4 Annual cases and incidence rate of reported enteroviral severe cases by age, 2000-2004, Taiwan

	2000		2001		2002		2003		2004	
	n	rate	n	rate	n	rate	n	rate	n	rate
<1year	106	37.9	118	44.1	70	29.2	30	13.3	26	12.4
1-	102	37.4	194	66.4	85	30.4	35	14.0	44	18.7
2-	89	30.3	112	41.0	62	21.2	26	9.29	23	9.20
3-	51	15.9	55	18.7	26	9.51	13	4.44	27	9.66
4-	43	13.4	44	13.7	19	6.47	8	2.93	16	5.47
5-9	35	2.17	58	3.61	32	1.99	15	0.95	9	0.59

Incidence rate=(cases/population size)*100000

Table 5 Annual incidence rates of reported enteroviral severe cases by year and gender in 2000-2004 in Taiwan

	Boys		Girls		Total	
year	n	incidence rate	n	incidence rate	n	incidence rate
2000	250	15.5	176	11.9	426	13.7
2001	351	22.0	230	15.7	581	19.0
2002	180	11.6	114	7.96	294	9.83
2003	76	5.03	51	3.67	127	4.38
2004	91	6.24	54	4.03	145	5.18

Table 6 Multvariates analysis for factors associated with enterovieal reported severe cases using Poisson regression model

Variables	RR	95%CI	P value
Gender			
Boys	1.39	1.26-1.54	<0.0001
Girls	1.00		
Age			
<1 year	16.2	13.3-19.8	<0.0001
1-	19.7	16.3-23.8	<0.0001
2-	12.8	10.5-15.6	<0.0001
3-	6.73	5.38-8.42	<0.0001
4-	4.95	3.90-6.30	<0.0001
5-9.9	1.00		
Region			
Northern	1.00		
Central	1.63	1.42-1.88	<0.0001
Southern	2.47	2.19-2.79	<0.0001
Eastern	1.17	0.81-1.69	0.3903
Month			
1	2.02	1.32-3.09	0.0011
2	1.00		
3	1.77	1.16-2.72	0.0083
4	2.53	1.66-3.87	<0.0001
5	4.30	2.80-6.58	<0.0001
6	4.34	2.81-6.71	<0.0001
7	3.14	2.01-4.94	<0.0001
8	3.07	1.95-4.82	<0.0001
9	3.05	1.97-4.74	<0.0001
10	3.60	2.36-5.49	<0.0001
11	2.94	1.95-4.43	<0.0001
12	2.36	1.57-3.55	<0.0001
Daily minimum temperature			
<10℃	1.34	0.62-2.92	0.4546
10-14.9	1.00		
15-19.9	1.18	0.91-1.54	0.2171
20-24.9	1.60	1.17-2.18	0.0033
≧25	1.63	1.15-2.30	0.0059

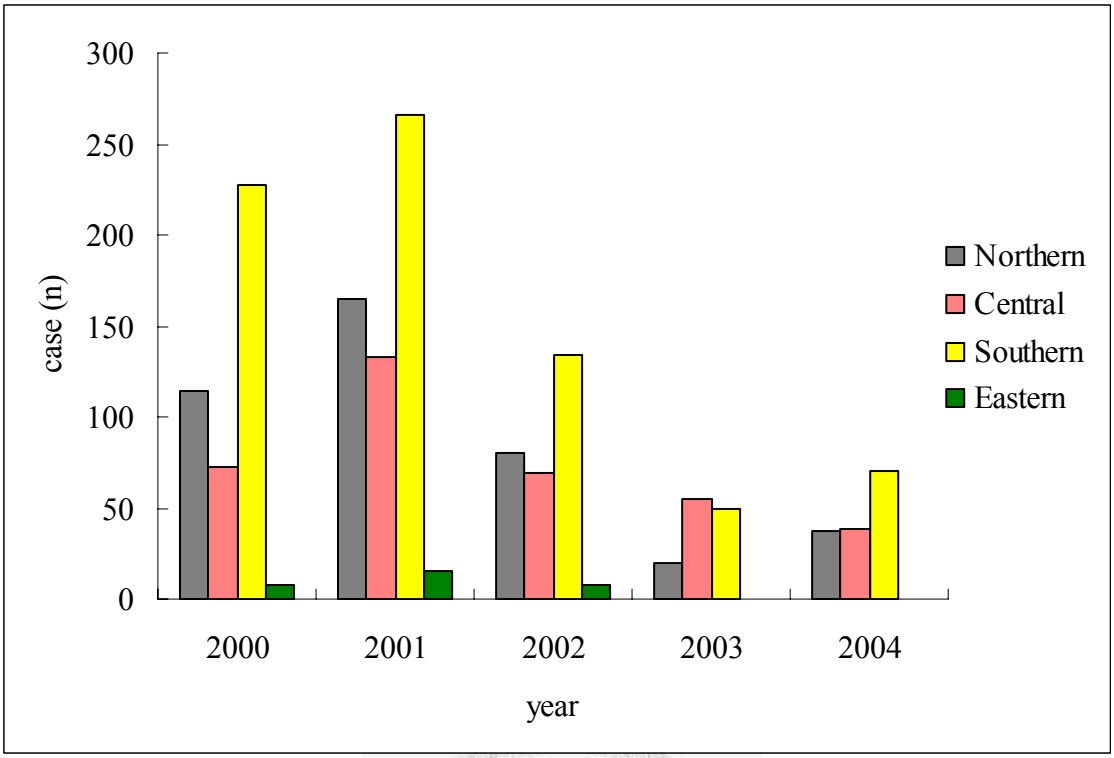


Figure 1- 1 Annual cases of reported enteroviral severe disease by region during 2000-2004 in Taiwan

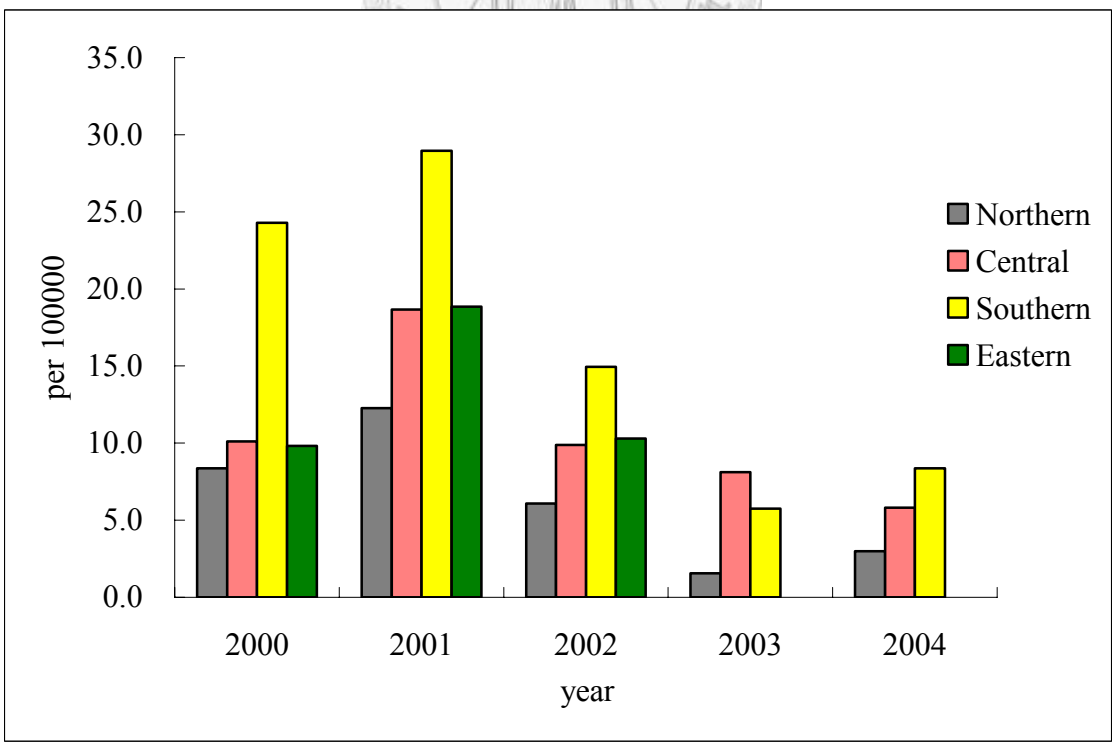


Figure 1- 2 Annual incidence rates of reported enteroviral severe cases by region during 2000-2004 in Taiwan

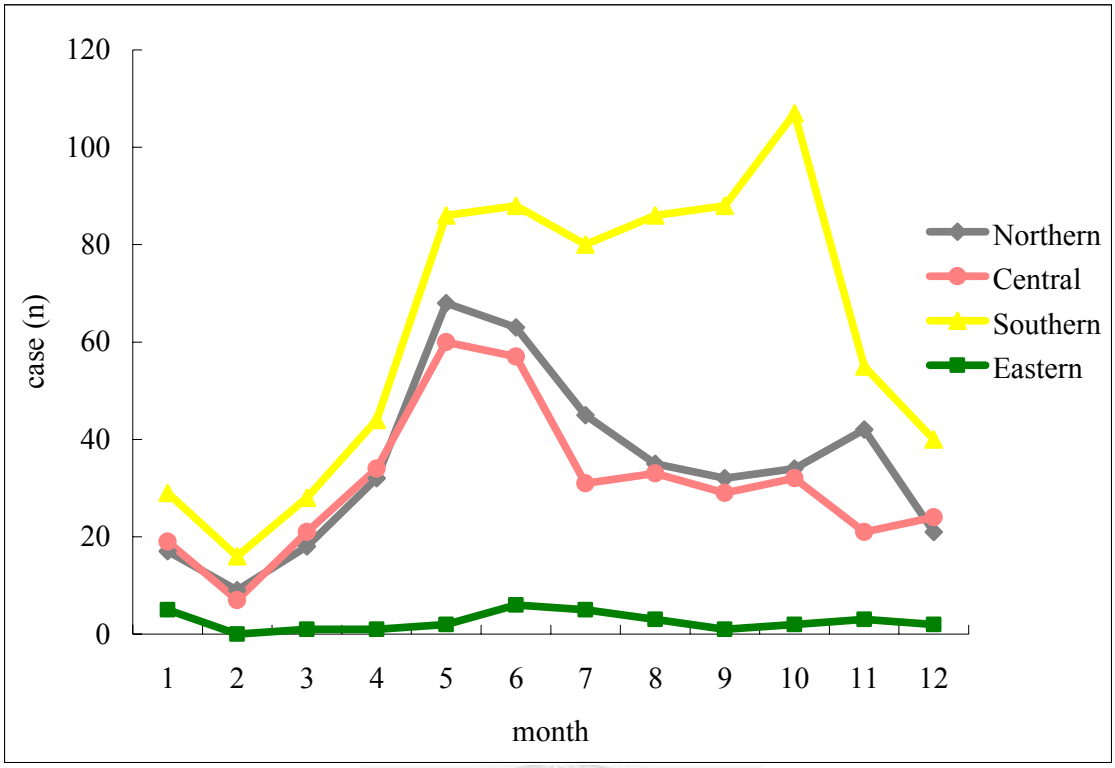


Figure 2- 1 Monthly cases of reported enteroviral severe disease by region in 2000-2004, Taiwan

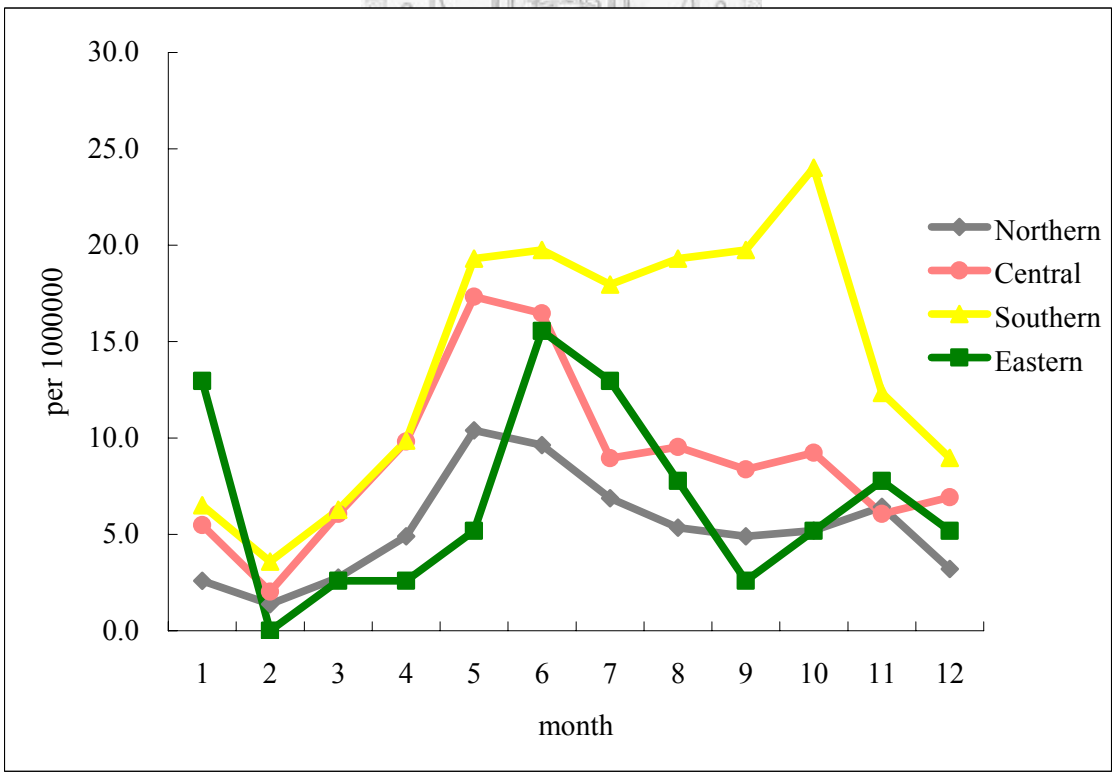


Figure 2- 2 Monthly incidence rates of reported enteroviral severe cases by region in 2000-2004, Taiwan

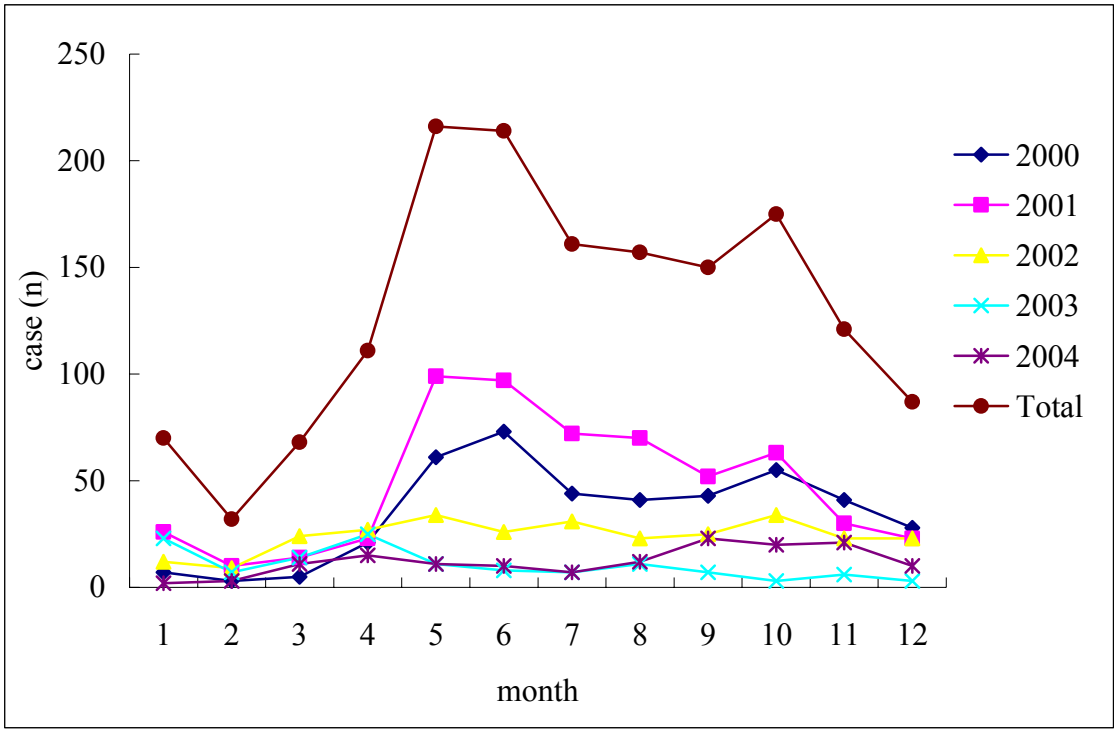


Figure 3- 1 Monthly cases of reported enteroviral severe disease by year 2000-2004

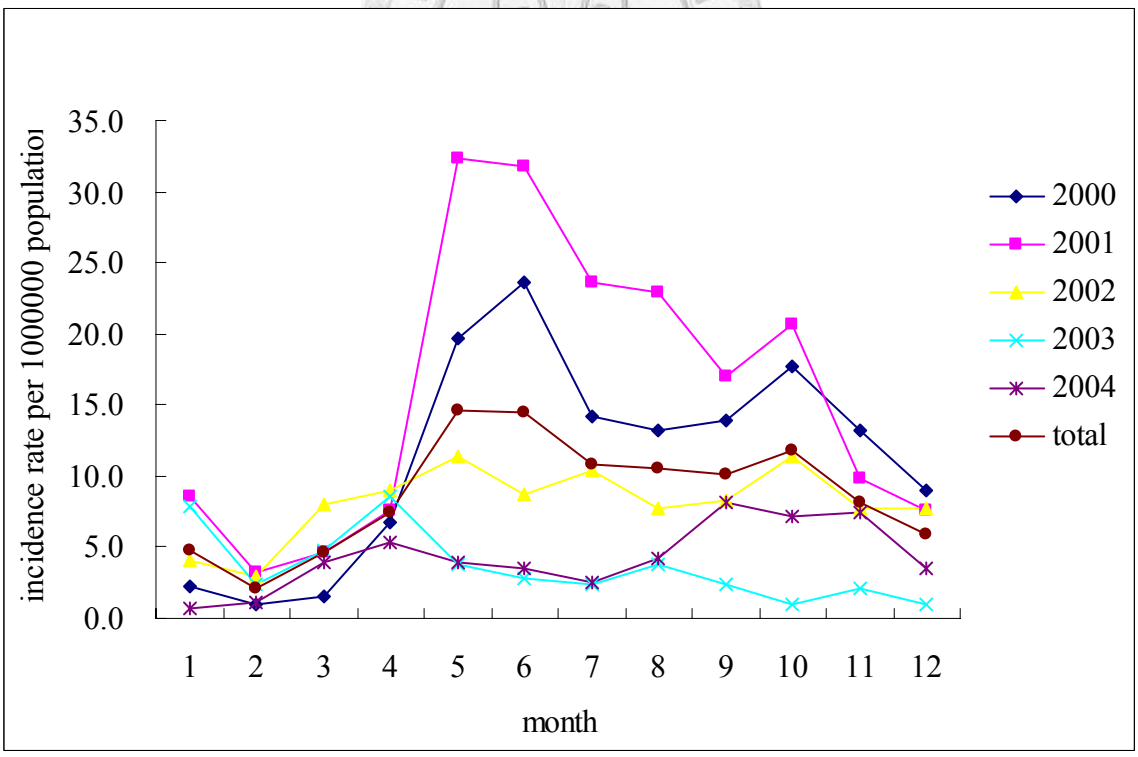


Figure 3- 2 Monthly incidence rate of reported enteroviral severe disease by year 2000-2004

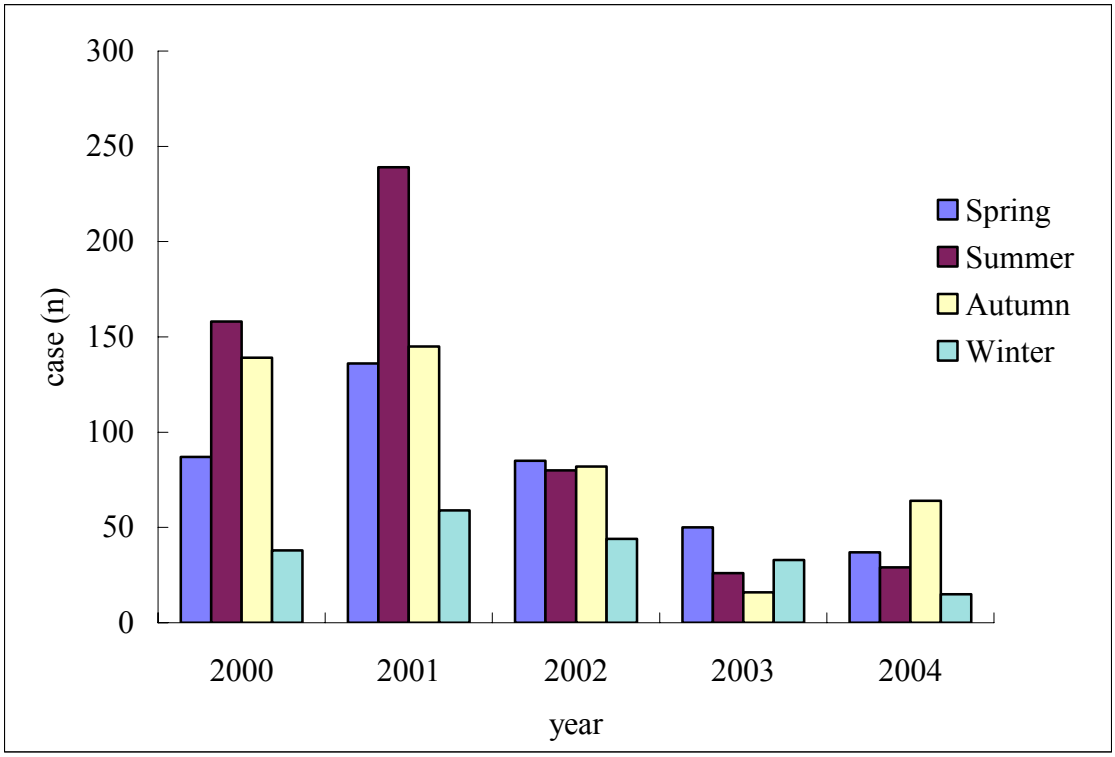


Figure 4- 1 Seasonal cases of reported enteroviral severe disease by year 2000-2004

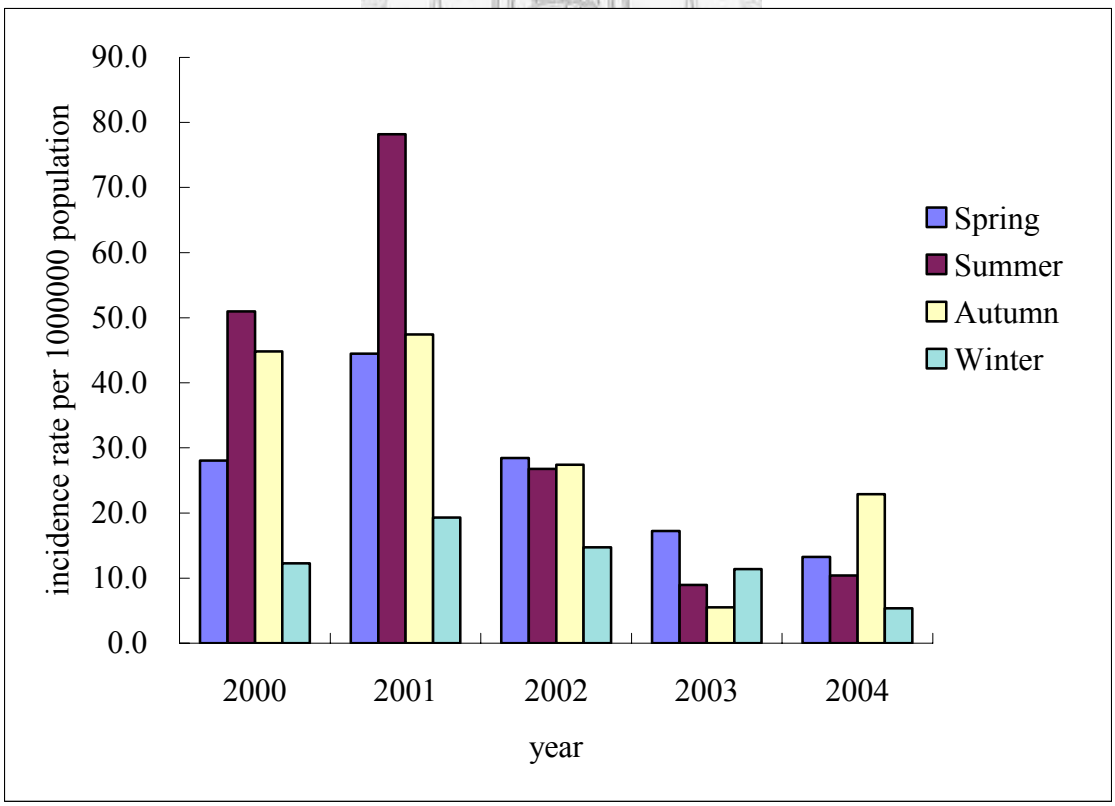


Figure 4- 2 Seasonal incidence rates of reported enteroviral severe disease by year 2000-2004

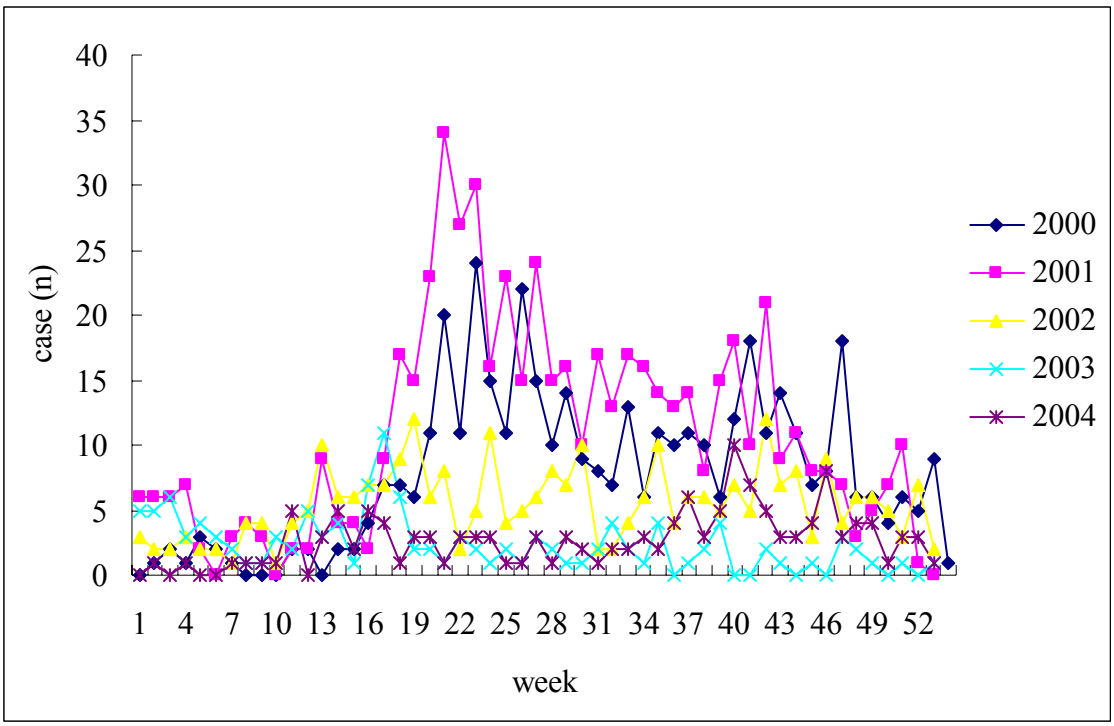


Figure 5 Weekly cases of reported enteroviral severe disease during 2000-2004 in Taiwan

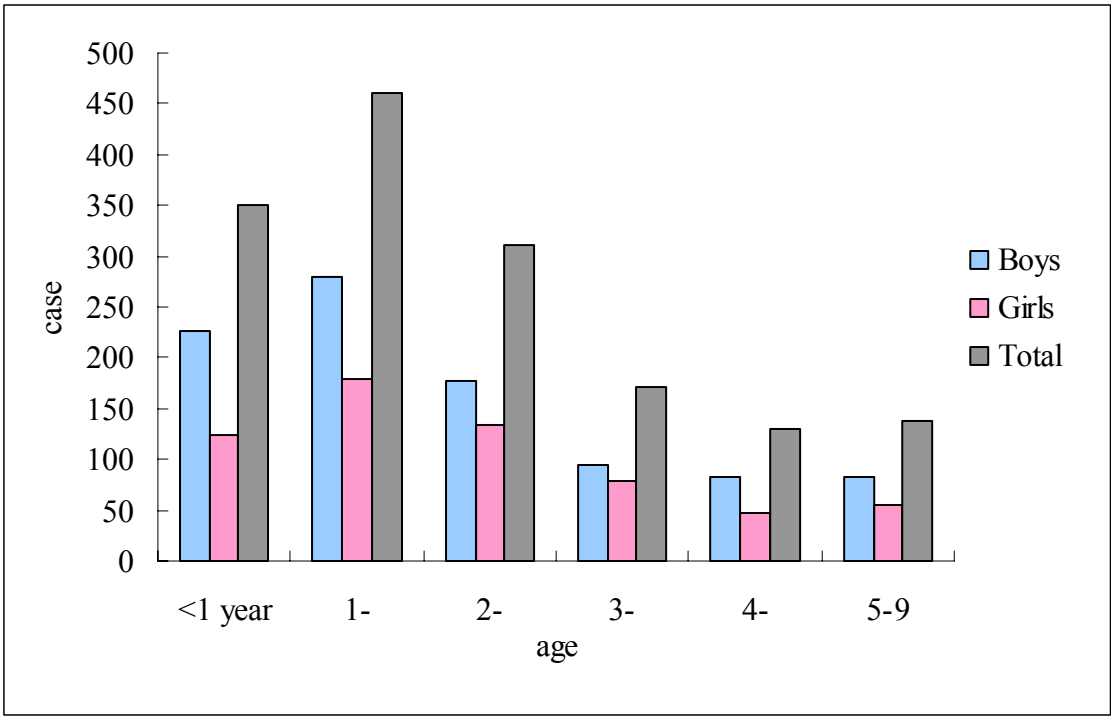


Figure 6- 1 Reported enteroviral severe cases by age in children younger than 10 years of age during 2000-2004 in Taiwan

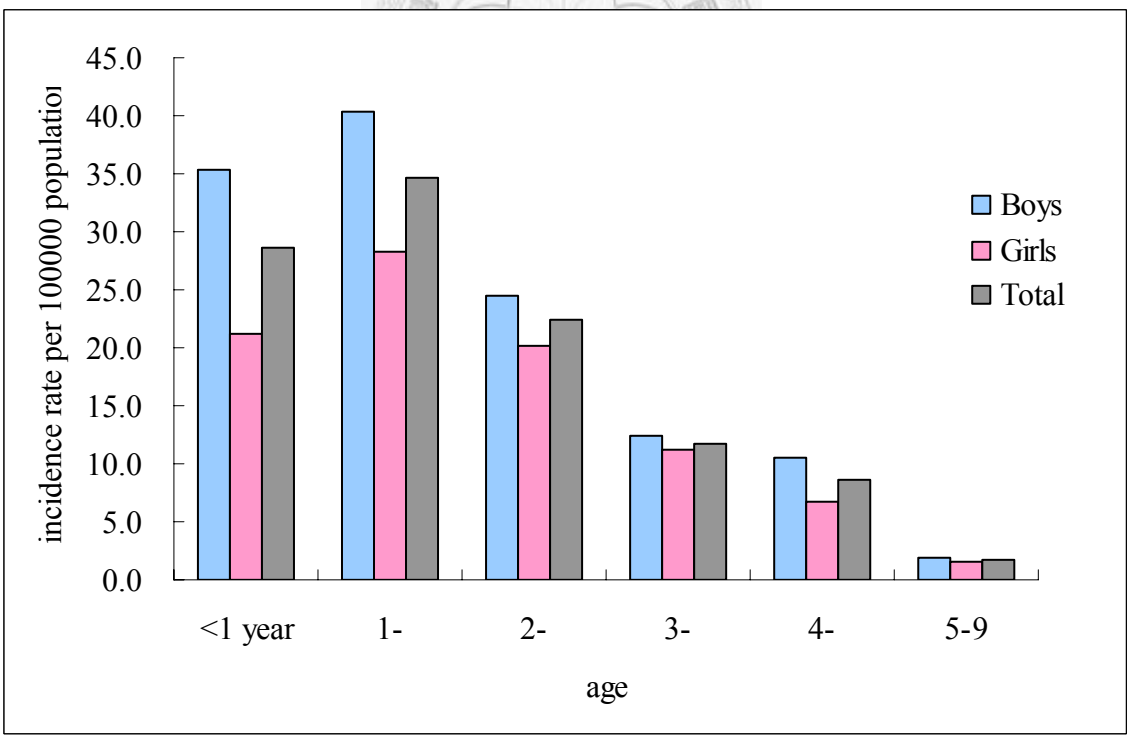


Figure 6- 2 Incidence rates of reported enteroviral severe cases by age in children younger than 10 years of age during 2000-2004 in Taiwan

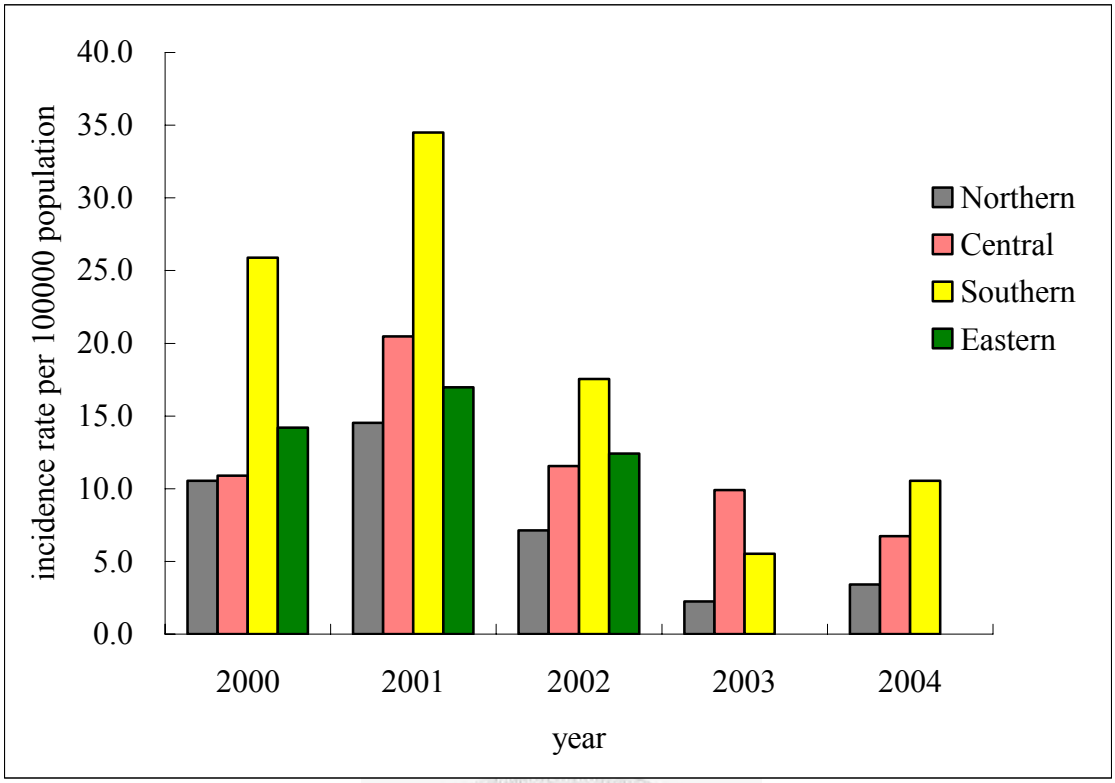


Figure 7- 1 Annual incidence of reported enteroviral severe cases of boys by region in2000-2004, Taiwan

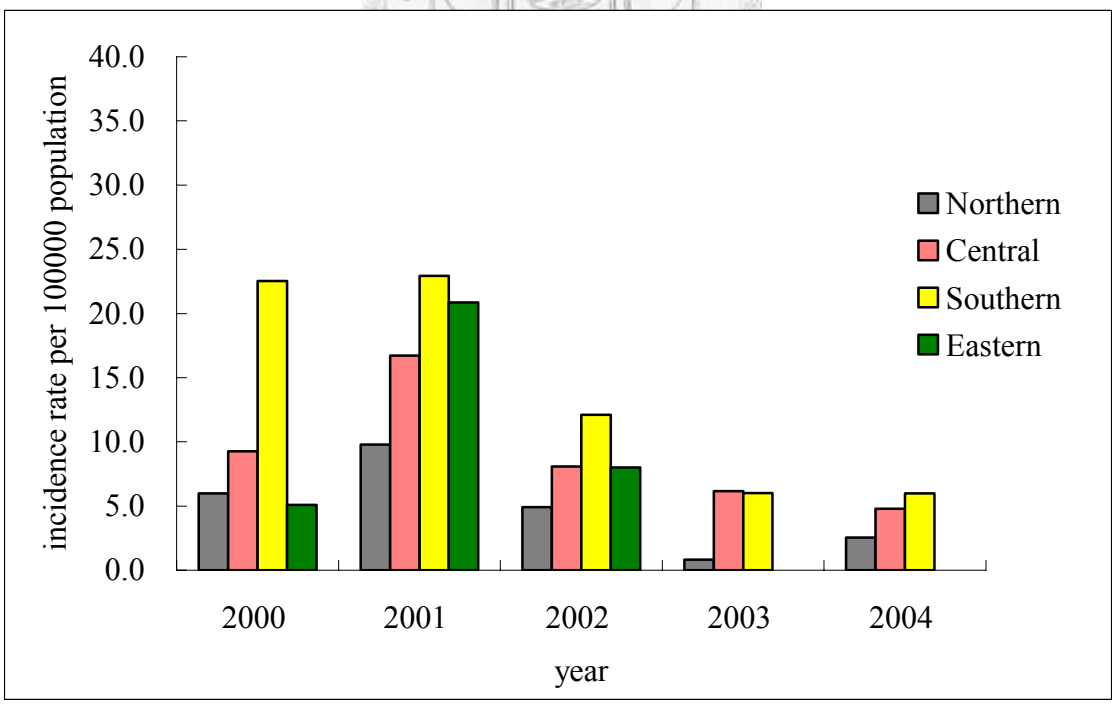


Figure 7- 2 Annual incidence rates of reported enteroviral severe cases of girls by region in 2000-2004, Taiwan

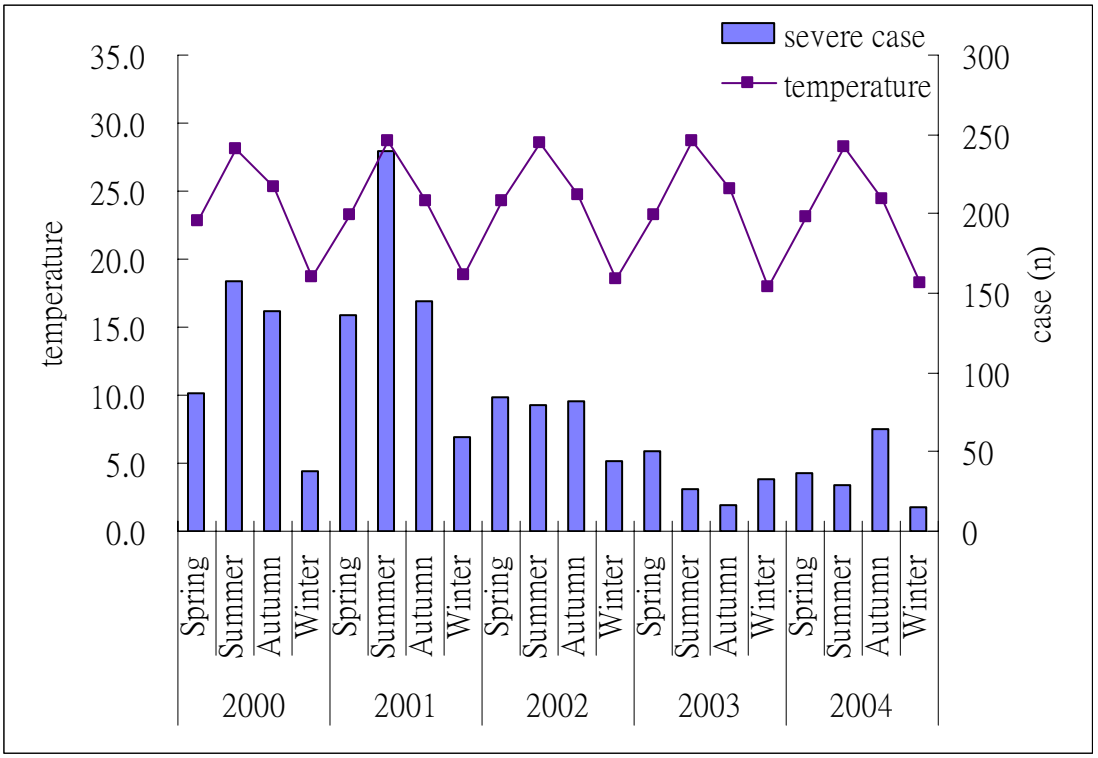


Figure 8- 1 Seasonal average temperature and reported enteroviral severe cases in 2000-2004, Taiwan

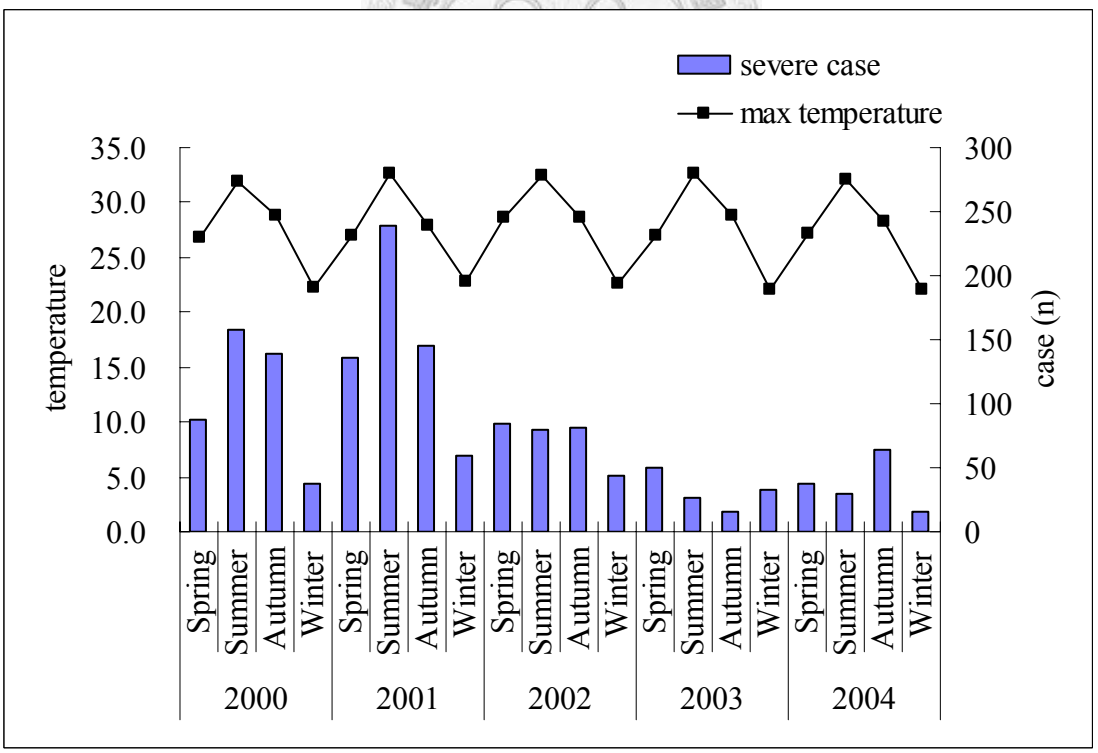


Figure 8- 2 Seasonal average maximum temperature and reported enteroviral severe cases in 2000-2004, Taiwan

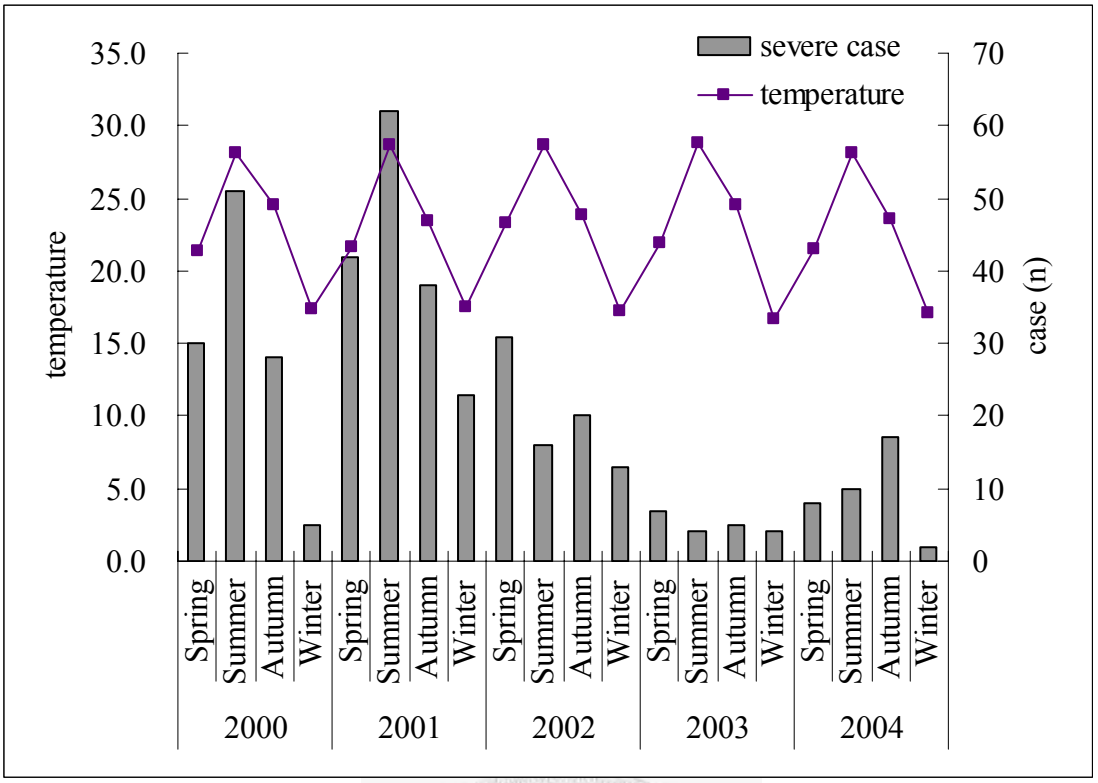


Figure 9- 1 Seasonal average temperature and reorted enteroviral severe cases in northern region in 2000-2004, Taiwan

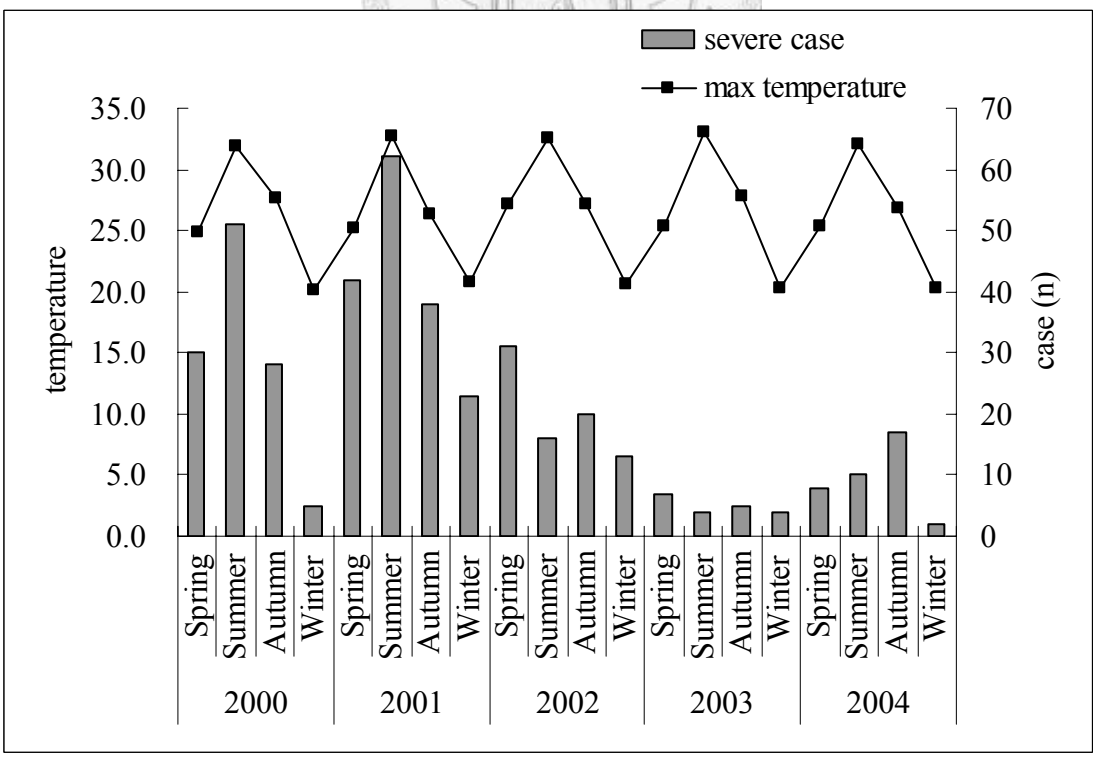


Figure 9- 2 Seasonal average maximum temperature and reported enteroviral severe cases in northern region in 2000-2004, Taiwan

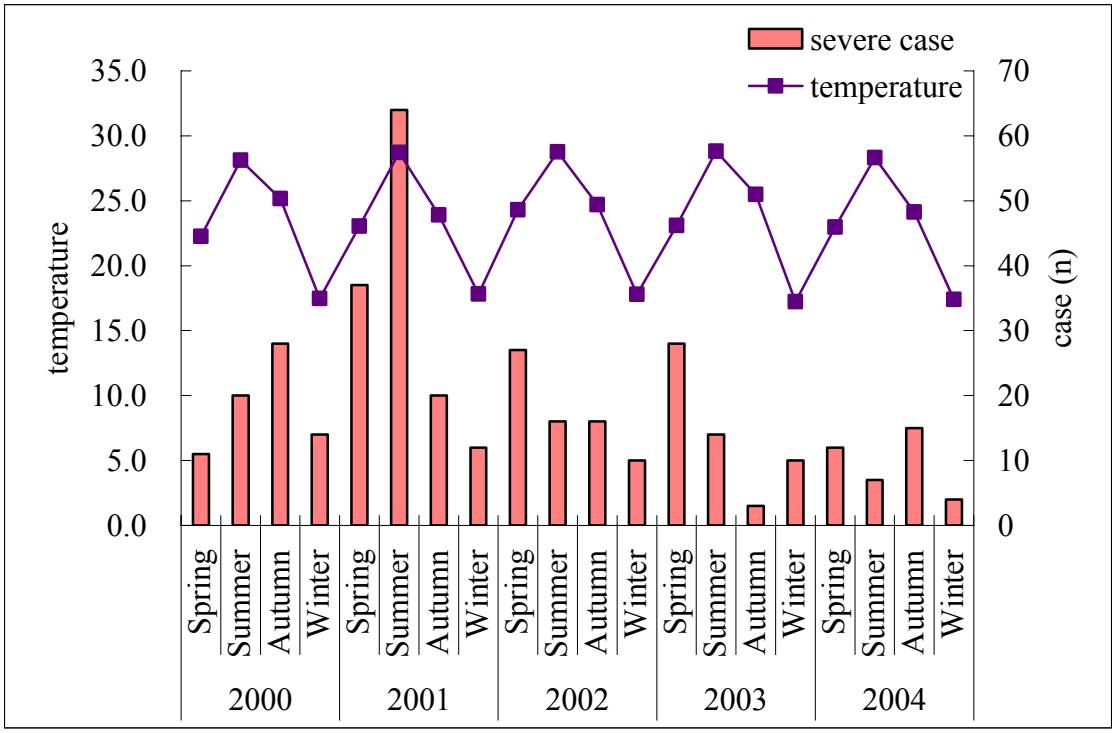


Figure 10- 1 Seasonal average temperature and reporte enteroviral severe cases in central region in 2000-2004, Taiwan

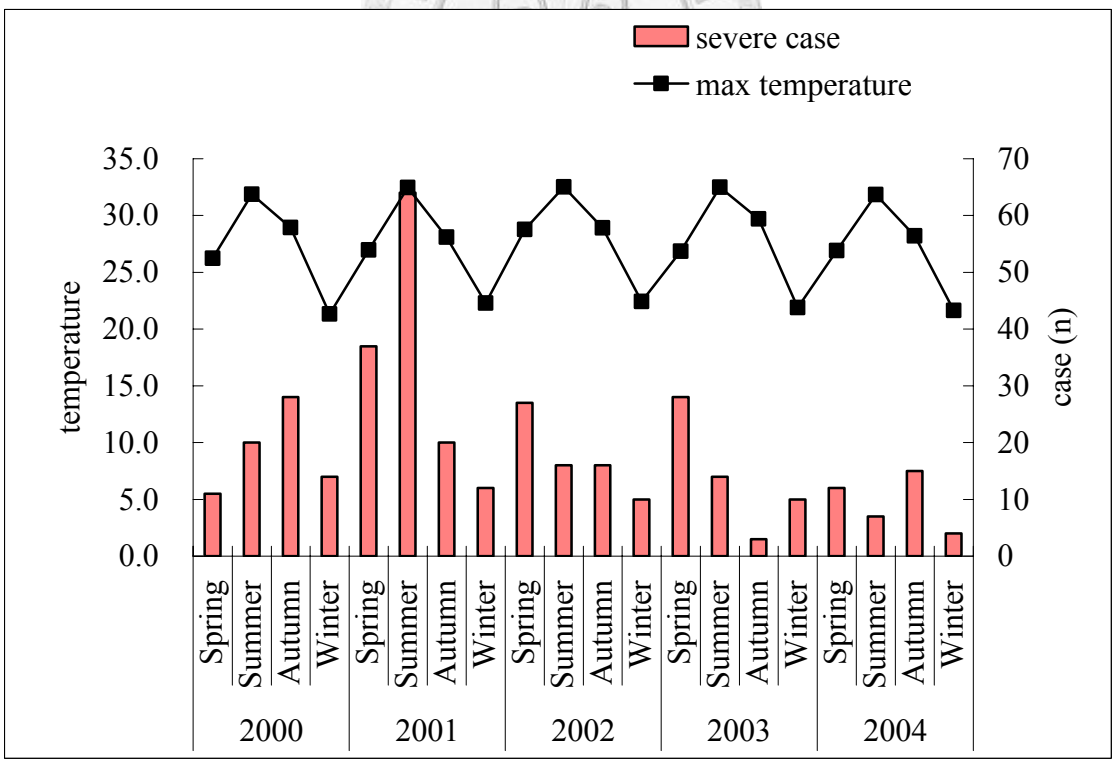


Figure 10- 2 Seasonal average maximum temperature and reported enteroviral severe cases in central region in 2000-2004, Taiwan

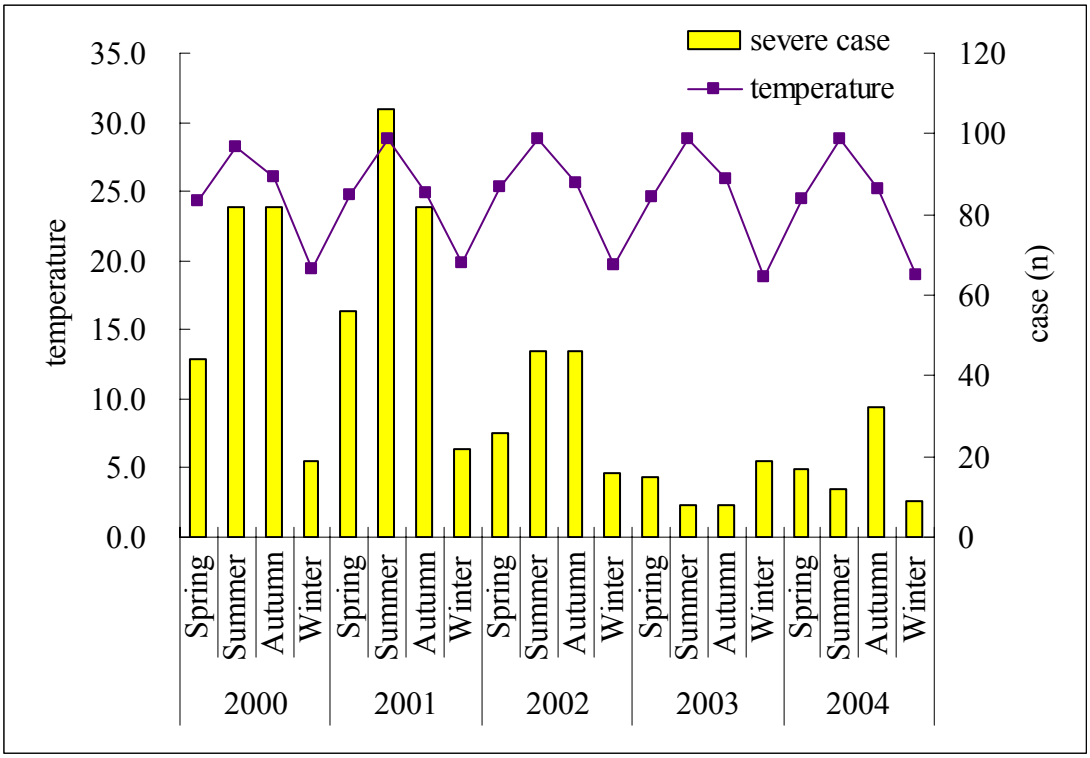


Figure 11- 1 Seasonal average temperature and reported enteroviral severe cases in southern region in 2000-2004, Taiwan

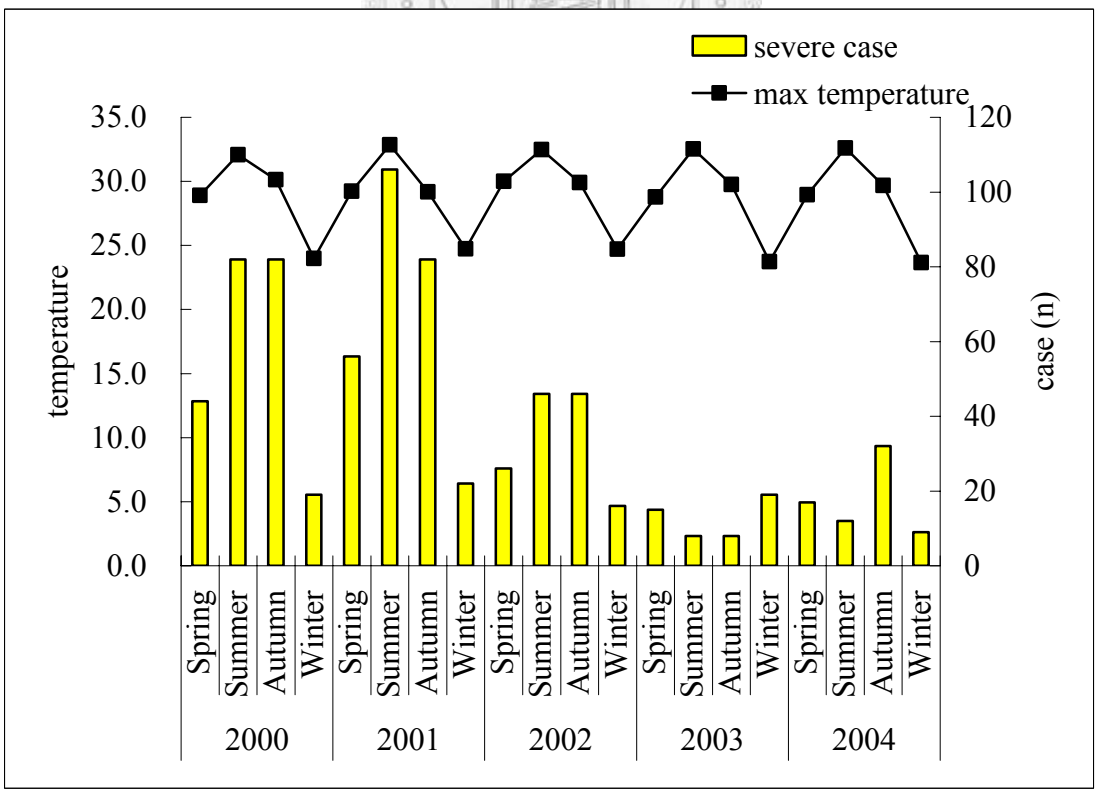


Figure 11- 2 Seasonal average maximum temperature and reported enteroviral severe cases in southern region in 2000-2004, Taiwan

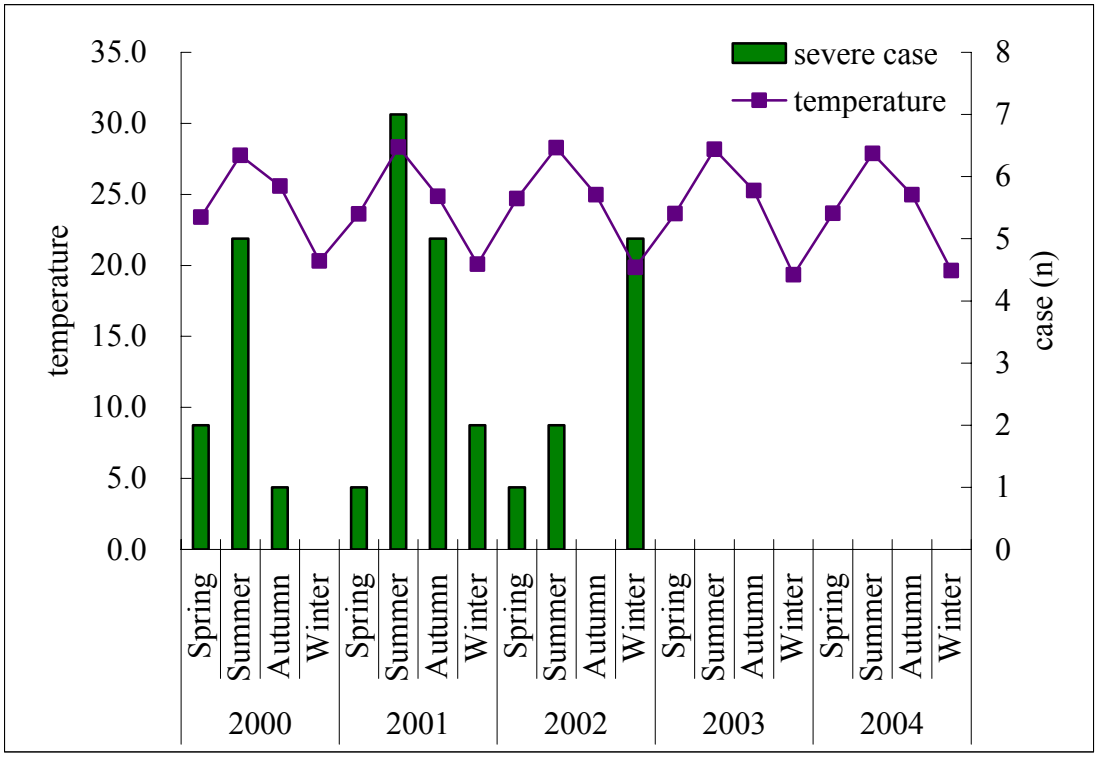


Figure 12- 1 Seasonal average temperature and reported enteroviral severe cases in eastern region in 2000-2004, Taiwan

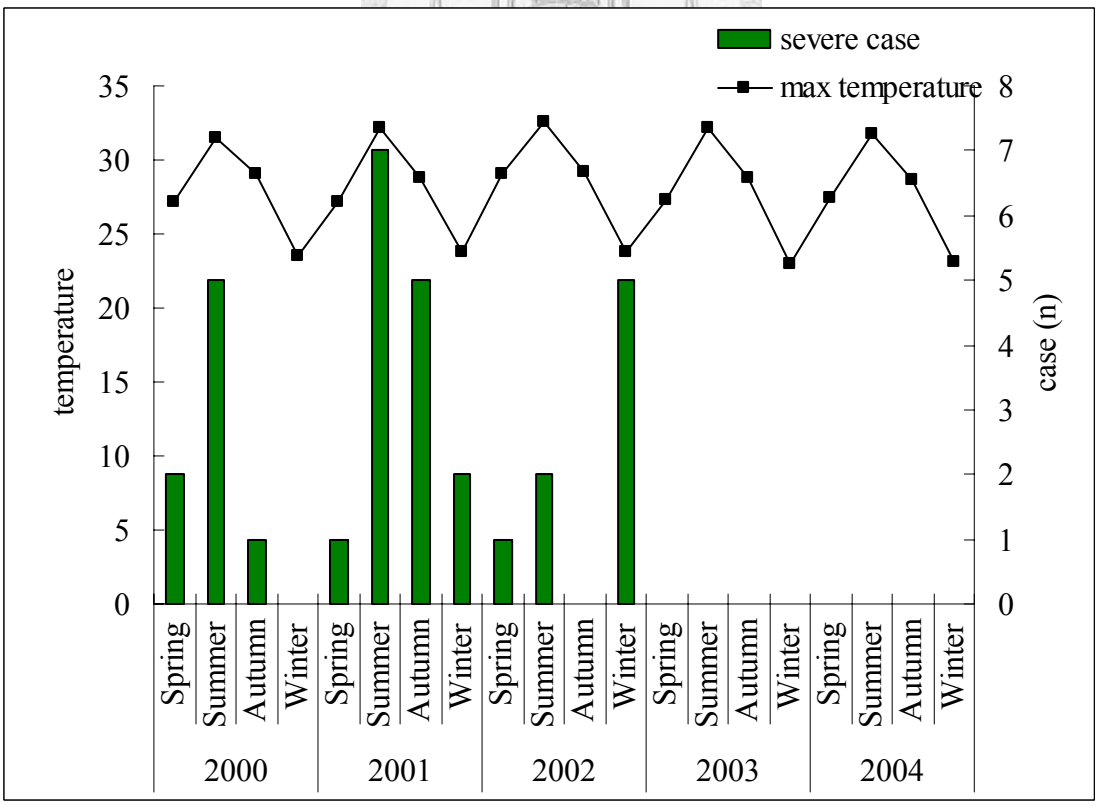


Figure 12- 2 Seasonal average maximum temperature and reported enteroviral severe cases in eastern region in 2000-2004, Taiwan

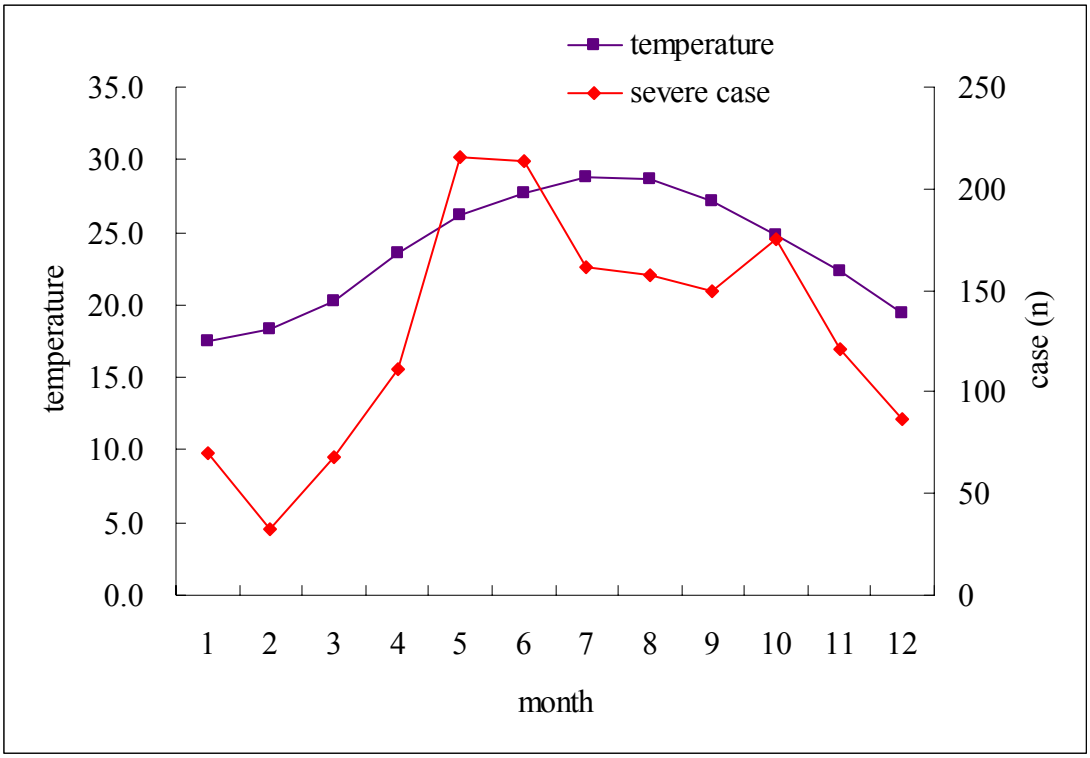


Figure 13-1 Monthly average temperature and reported enteroviral severe cases in 2000-2004, Taiwan

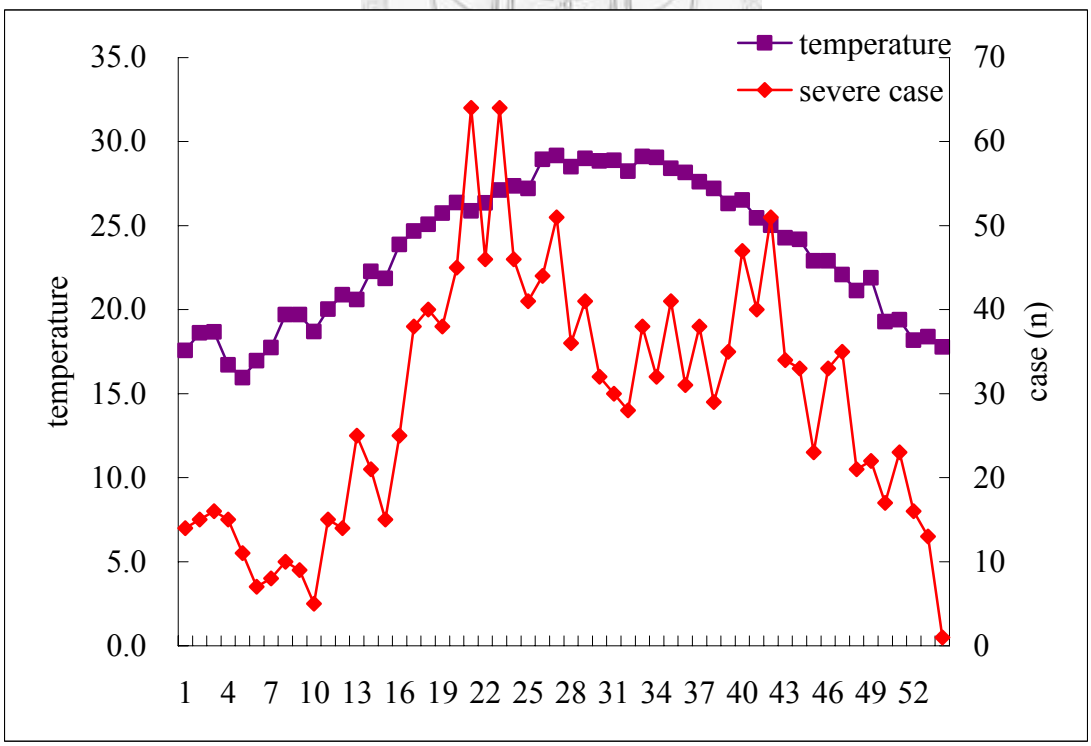


Figure 13-2 Weekly average temperature and reported enteroviral severe cases in 2000-2004, Taiwan

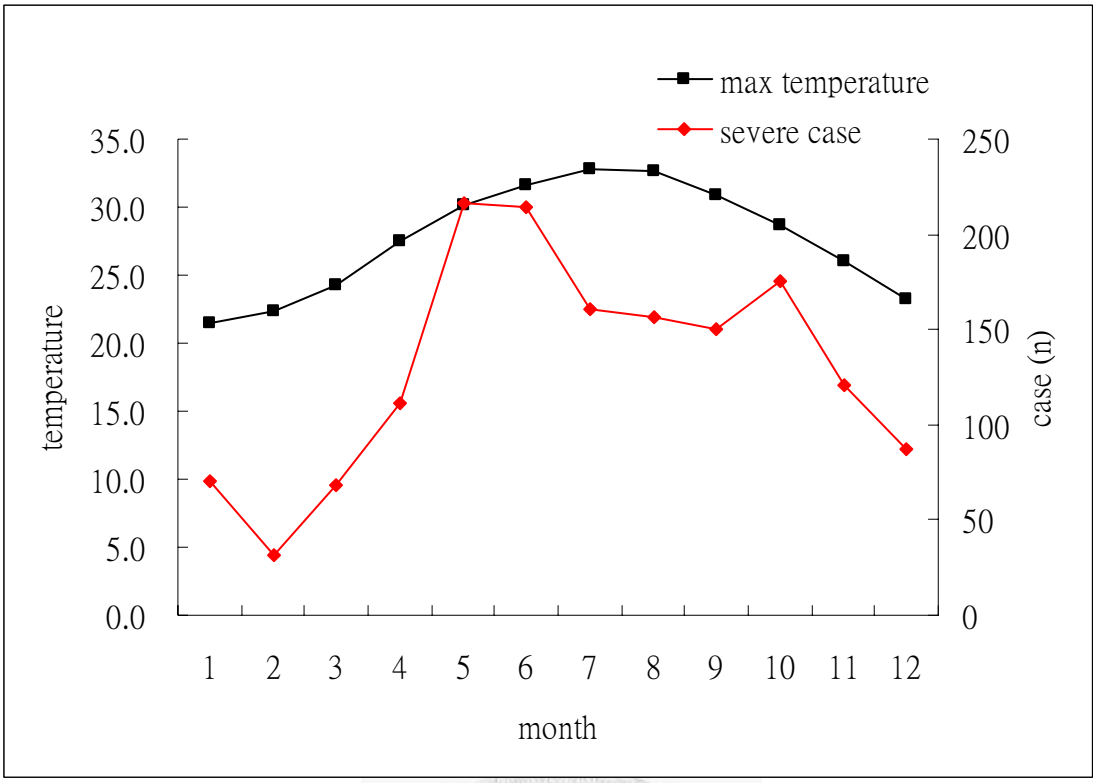


Figure 14- 1 Monthly average maximum temperature and enteroviral reported severe cases in 2000-2004, Taiwan

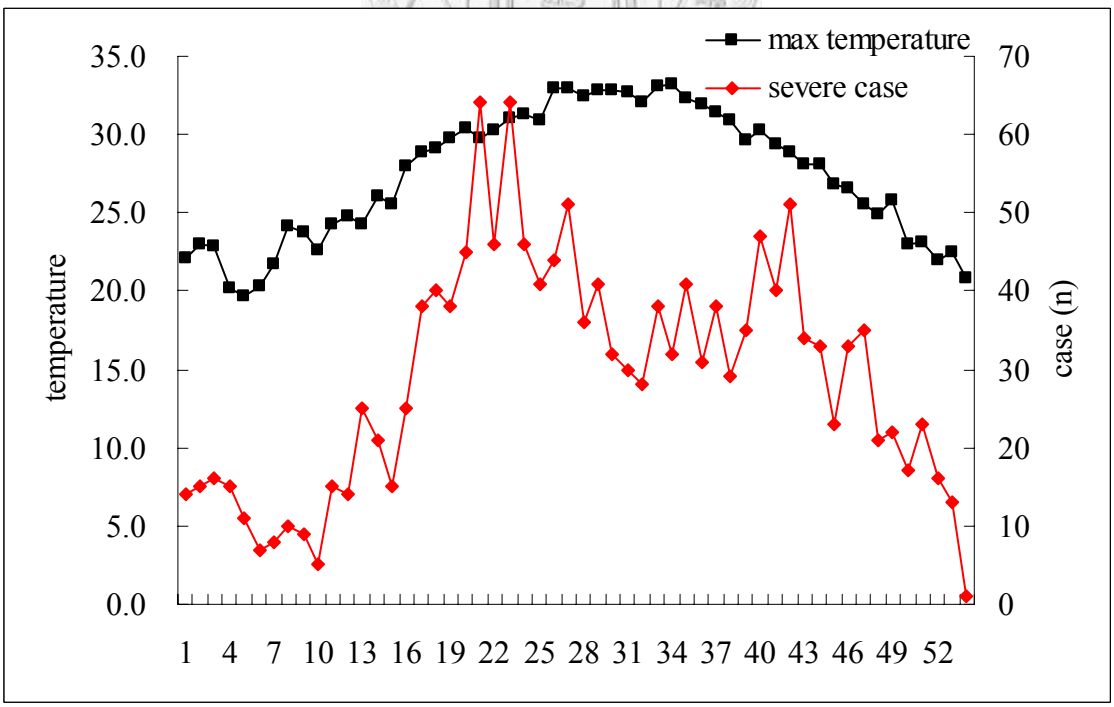


Figure 14- 2 Average highest daily temperature by week and total weekly reported enteroviral severe cases in 2000-2004, Taiwan

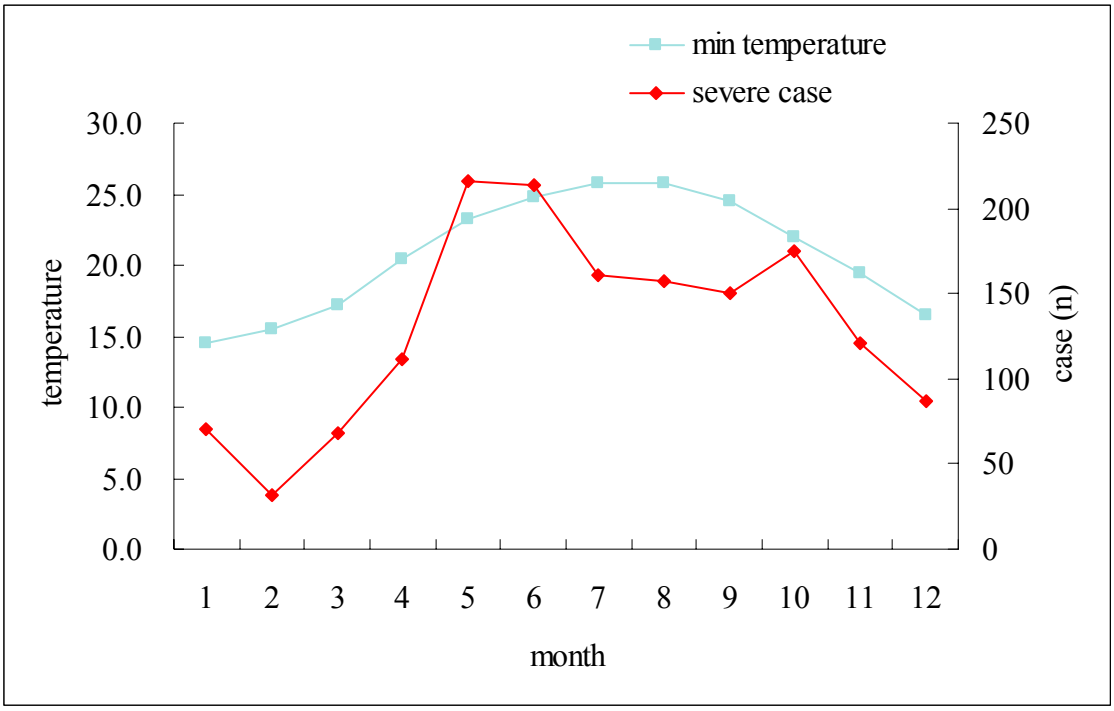


Figure 15- 1 Monthly average minimum temperature and reported enteroviral severe cases in 2000-2004, Taiwan

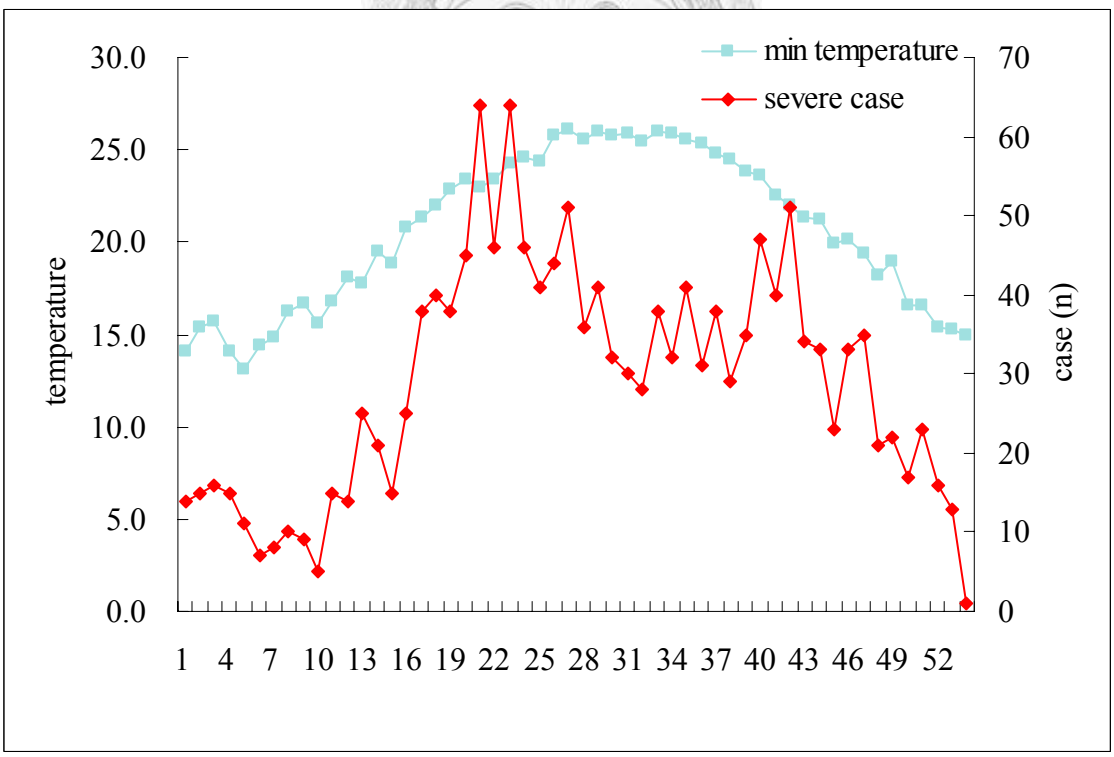


Figure 15- 2 Average lowest daily temperature by week and total weekly reported enteroviral severe cases in 2000-2004, Taiwan

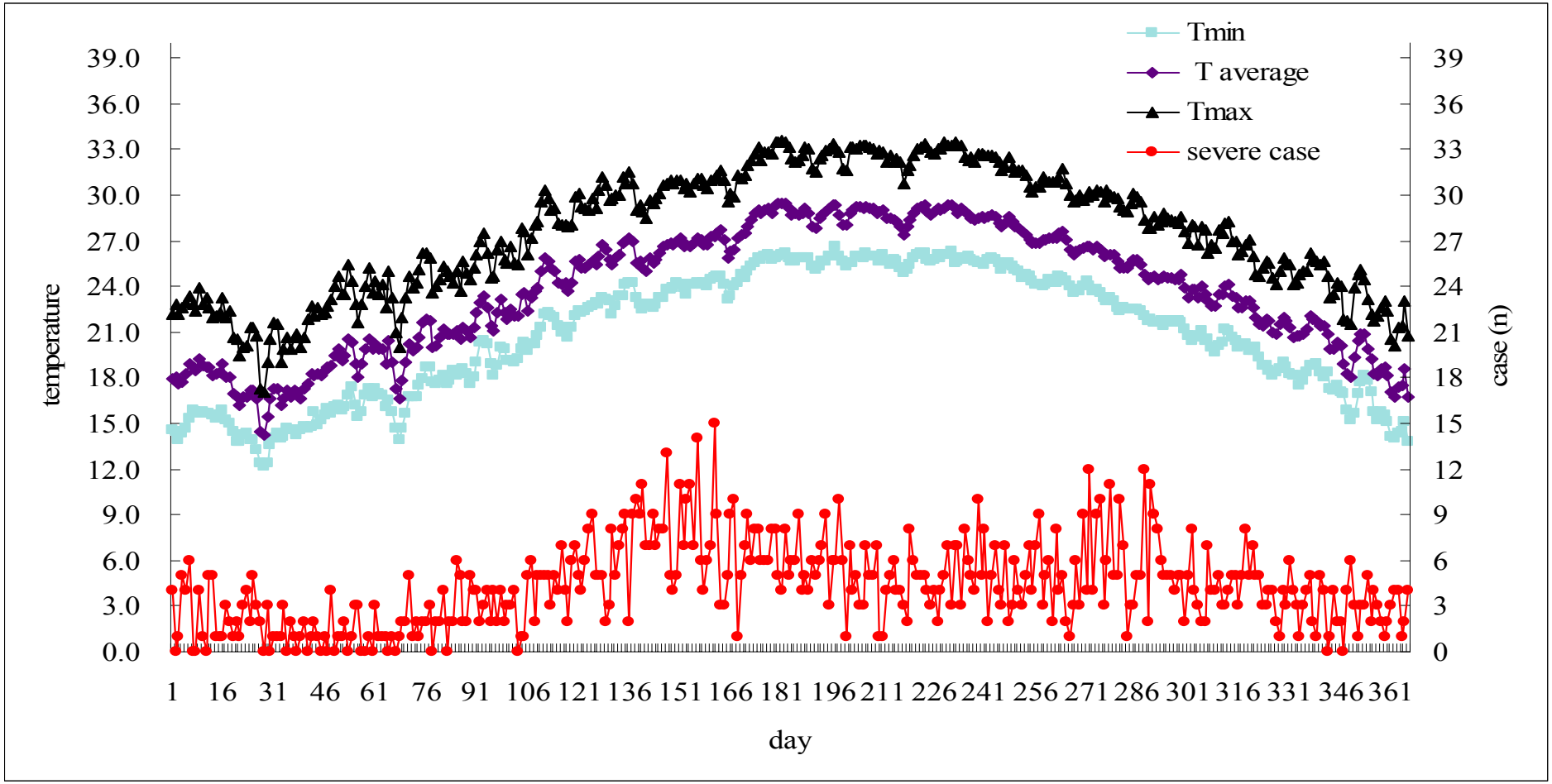


Figure 16 Average daily temperature, average daily maximum and minimum temperature related to daily total reported enteroviral severe cases in 000-2004, Taiwan

Appendix 4

Sentinel physicians reported cases

Table 1 Univariate Poisson regression analysis for the risk of HFMD and herpangina reported by sentinel physicians associated with region, year, and month

Variables		RR	95% CI	P value
Region				
	Northern	1.00		
	Central	2.41	2.40-2.43	<0.0001
	Southern	2.28	2.26-2.29	<0.0001
	Eastern	3.52	3.47-3.56	<0.0001
Year				
	2000	1.47	1.46-1.49	<0.0001
	2001	1.20	1.19-1.22	<0.0001
	2002	1.00		
	2003	1.01	1.00-1.02	0.0026
	2004	1.03	1.02-1.04	<0.0001
Month				
	1	1.49	1.46-1.52	<0.0001
	2	1.00		
	3	1.73	1.70-1.77	<0.0001
	4	3.77	3.70-3.84	<0.0001
	5	6.48	6.37-6.60	<0.0001
	6	6.11	6.01-6.22	<0.0001
	7	3.46	3.40-3.53	<0.0001
	8	2.41	2.37-2.46	<0.0001
	9	2.66	2.61-2.71	<0.0001
	10	2.63	2.58-2.68	<0.0001
	11	2.59	2.55-2.65	<0.0001
	12	2.07	2.04-2.12	<0.0001

Table 2 Univariate Poisson regression analysis for the risk of sentinel physicians reported HFMD and herpangina reported cases associated with weather status

Variables	RR	95% CI	P value
Average weekly temperature			
<15℃	1.00		
15-19.9	1.58	1.53-1.62	<0.0001
20-24.9	3.15	3.06-3.24	<0.0001
25-29.9	4.71	4.58-4.85	<0.0001
≧30	3.64	3.50-3.78	<0.0001
Weekly maximum temperature			
<15℃	1.00		
15-19.9	2.19	1.94-2.48	<0.0001
20-24.9	3.71	3.28-4.19	<0.0001
25-29.9	7.57	6.70-8.56	<0.0001
≧30	9.45	8.36-10.7	<0.0001
Weekly minimum temperature			
<10℃	1.00		
10-14.9	1.66	1.49-1.85	<0.0001
15-19.9	2.59	2.33-2.88	<0.0001
20-24.9	5.74	5.16-6.39	<0.0001
>25	4.64	4.17-5.16	<0.0001
Average weekly rainfall hours			
0-4.9 hrs	1.00		
5-9.9	0.67	0.66-0.67	<0.0001
10-14.9	0.49	0.48-0.51	<0.0001
≧15	0.18	0.16-0.21	<0.0001
Average weekly sunshine hours			
0-2.49 hrs	1.00		
2.5-4.99	1.47	1.46-1.49	<0.0001
5.0-7.49	1.79	1.77-1.81	<0.0001
7.5-9.99	1.88	2.86-1.90	<0.0001
≧10	2.20	2.14-2.26	<0.0001

Table 3 Severe enteroviral infection cases to sentinel physicians reported HFMD and herpangina cases ratio by year in 2000-2004, Taiwan

Year	Severe cases	physicians reported	Ratio x 10^{-4}
2000	286	135565	21.1
2001	391	111486	35.1
2002	162	93048	17.4
2003	70	94764	7.39
2004	50	97002	5.15
Total	959	531865	18.0

Table 4 Severe enteroviral infection cases to sentinel physicians reported HFMD and herpangina cases ratio by region in 2000-2004, Taiwan

Region	Severe cases	physicians reported	Ratio x 10-^{4}
Northern	277	129960	21.3
Central	251	158480	15.8
Southern	407	215355	18.9
Eastern	24	28070	8.55
Total	959	531865	18.0

Table 5 Severe enteroviral infection cases to sentinel physicians reported HFMD and herpangina cases ratio by month in 2000-2004, Taiwan

Month	Severe cases	physicians reported	Ratio x 10^{-4}
1	42	21729	19.3
2	15	14594	10.3
3	30	25275	11.9
4	66	55057	12.0
5	129	94638	13.6
6	142	89216	15.9
7	100	50551	19.8
8	97	35259	27.5
9	94	38843	24.2
10	116	38439	30.2
11	76	37937	20.0
12	52	30327	17.2
Total	959	531865	18.0

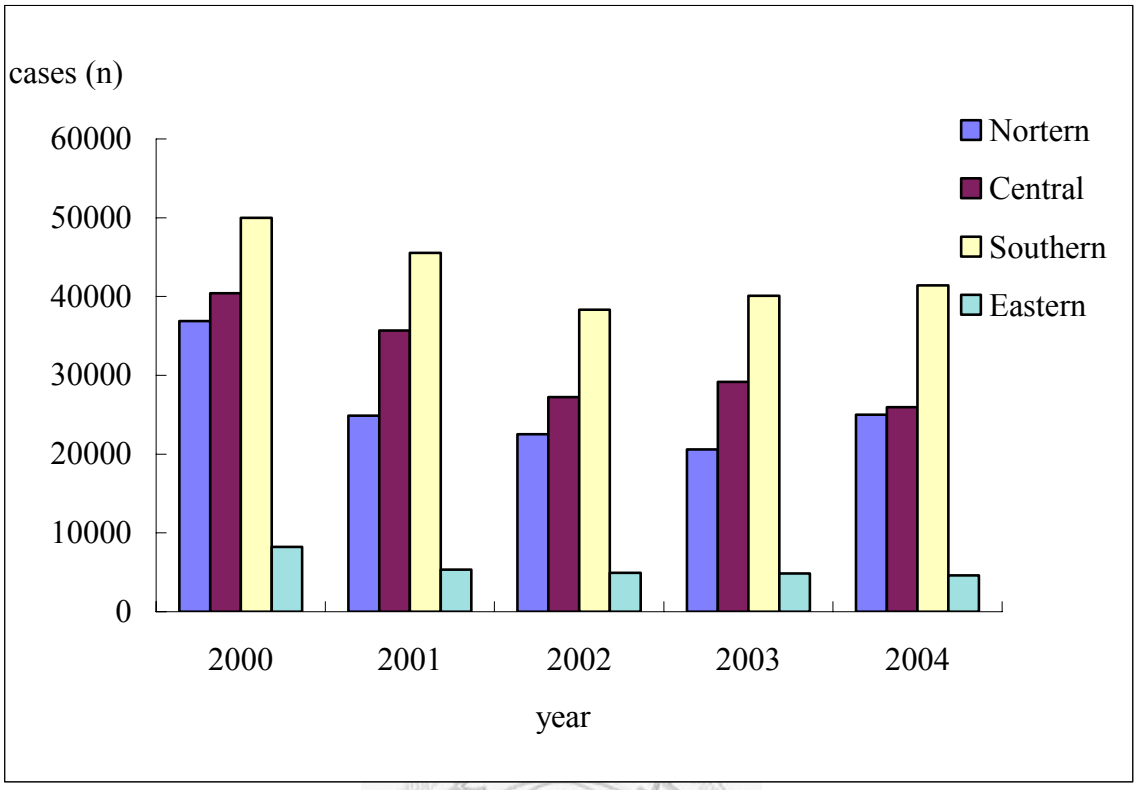


Figure 1 Total cases of HFMD and herpangina reported by sentinel physicians by region in 2000-2004 Taiwan

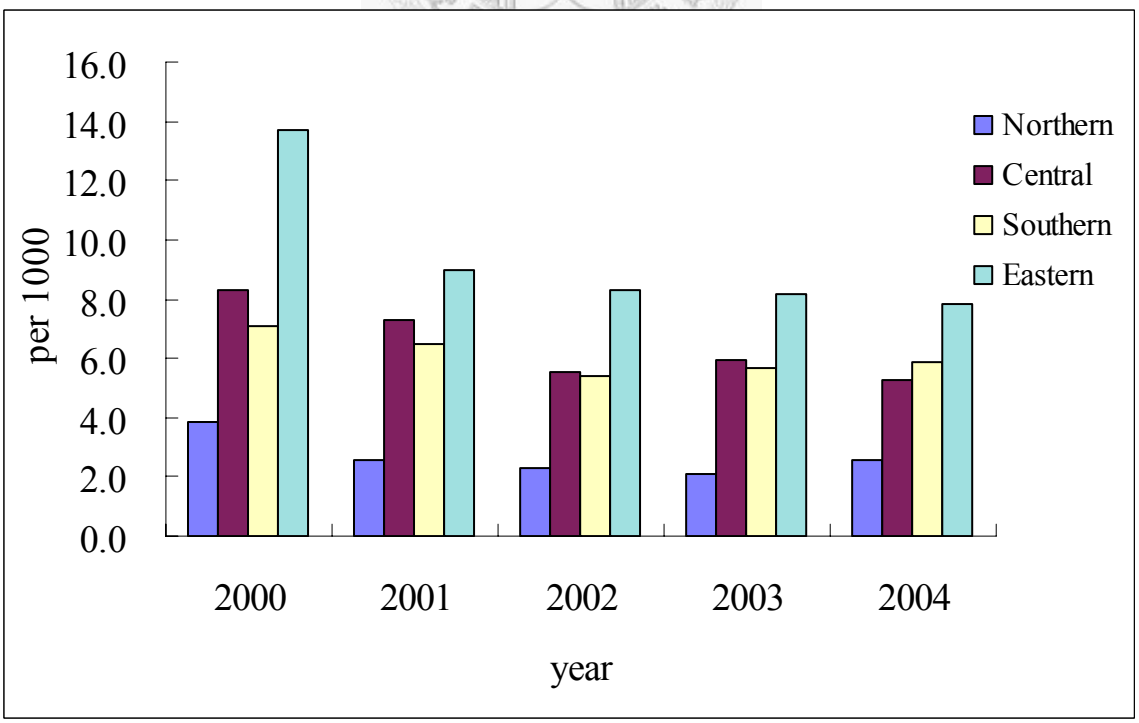


Figure 2 Rate of enteroviral infection cases reported by sentinel physicians by region in 2000-2004, Taiwan

Appendix 5

Virology laboratory tested

Table 1 Enteroviral laboratory test positive rates by age and gender in 2000-2004, Taiwan

	Boys		Girls		Total	
	n	rate	n	rate	n	rate
<1 year	347	37.2	262	39.5	609	38.2
1-	450	40.3	336	39.6	786	40.0
2-	342	45.1	243	40.8	585	43.2
3-	245	47.9	178	42.5	423	45.4
4-	208	48.6	154	44.6	362	46.8
5-9	305	47.0	243	43.6	548	45.4
Total	1897	43.1	1416	41.3	3313	42.3

positive rate=(case/reported as enterovirus case)*100

Table 2 Age-specific proportional distribution of laboratory confirmed enteroviral infection by region in 2000-2004, Taiwan

	Region				Total
	Northern	Central	Southern	Eastern	
	n (%)	n (%)	n (%)	n (%)	n (%)
<1 year	143 (14.1)	163 (15.1)	293 (25.9)	10 (11.2)	609 (18.4)
1-	231 (22.7)	292 (27.1)	237 (21.0)	26 (29.2)	786 (23.7)
2-	189 (18.6)	209 (19.4)	170 (15.0)	17 (19.1)	585 (17.7)
3-	130 (12.8)	127 (11.8)	154 (13.6)	12 (13.5)	423 (12.8)
4-	138 (13.6)	98 (9.10)	116 (10.3)	10 (11.2)	362 (10.9)
5-9	186 (18.3)	187 (17.4)	161 (14.2)	14 (15.7)	548 (16.5)
Total	1017 (100)	1076 (100)	1131 (100)	89 (100)	3313 (100)

Table 3 Age-specific laboratory test positive rates by age and region in 2000-2004, Taiwan

	Region				Total
	Northern	Central	Southern	Eastern	
<1 year	34.4	35.1	44.3	19.2	38.2
1-	42.8	44.2	34.8	30.2	40.0
2-	47.5	44.9	39.3	29.3	43.2
3-	44.4	49.0	46.0	27.3	45.4
4-	55.2	41.9	46.6	25.0	46.8
5-9	46.9	49.3	42.6	26.9	45.4
Total	44.3	43.7	41.3	26.8	42.3

positive rate=(case/reported as enterovirus case)*100

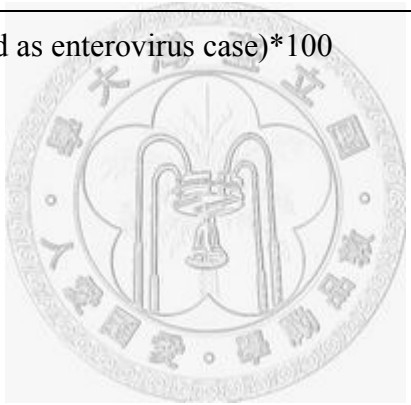


Table 4 Univariate Poisson regression analysis for association between laboratory enteroviral positive test and gender, age and region

Variables		RR	95% CI	P value
Gender				
	Boy	1.04	0.98-1.12	0.2125
	Girl	1.00		
Age				
	<1 year	0.84	0.75-0.94	0.0031
	1-	0.88	0.79-0.98	0.0209
	2-	0.95	0.85-1.07	0.3964
	3-	1.00	0.88-1.14	0.9988
	4-	1.03	0.90-1.18	0.6562
	5-9	1.00		
Region				
	Northern	1.00		
	Central	0.99	0.90-1.07	0.7440
	Southern	0.93	0.86-1.01	0.1019
	Eastern	0.60	0.49-0.75	<0.0001

Table 5 Univariate Poisson regression analysis for laboratory enteroviral positive test associated with epidemic year, season and month

Variables		RR	95% CI	P value
Year				
	2000	0.38	0.34-0.42	<0.0001
	2001	0.50	0.45-0.54	<0.0001
	2002	0.34	0.29-0.40	<0.0001
	2003	0.50	0.46-0.55	<0.0001
	2004	1.00		
Season				
	Spring	1.51	1.35-1.69	<0.0001
	Summer	1.12	0.99-1.26	0.0626
	Autumn	1.11	0.99-1.25	0.0803
	Winter	1.00		
Month				
	1	1.03	0.80-1.32	0.8443
	2	1.00		
	3	1.46	1.16-1.85	0.0015
	4	1.79	1.45-2.22	<0.0001
	5	1.52	1.24-1.87	<0.0001
	6	1.24	1.00-1.54	0.0487
	7	1.20	0.96-1.49	0.1103
	8	1.09	0.87-1.37	0.4610
	9	1.24	0.99-1.56	0.0610
	10	1.08	0.86-1.36	0.5145
	11	1.22	0.97-1.52	0.0850
	12	1.13	0.89-1.45	0.3151

Table 6 Univariate Poisson regression analysis for laboratory enteroviral positive test associated with weather parameters

Variables	RR	95% CI	P value
Average daily temperature			
<15℃	1.00		
15-19.9	0.96	0.76-1.22	0.7440
20-24.9	1.10	0.88-1.37	0.3892
25-29.9	1.04	0.84-1.29	0.7047
≧30	0.91	0.67-1.23	0.5323
Daily maximum temperature			
<15℃	1.00		
15-19.9	1.28	0.76-2.15	0.3450
20-24.9	1.25	0.76-2.06	0.3775
25-29.9	1.37	0.84-2.25	0.2105
≧30	1.32	0.81-2.16	0.2679
Daily minimum temperature			
<10℃	1.00		
10-14.9	1.33	0.67-2.59	0.3945
15-19.9	1.54	0.80-2.98	0.1945
20-24.9	1.55	0.81-2.99	0.1877
≧25	1.46	0.76-2.81	0.2619
Average daily rainfall hours			
0-4.9 hrs	1.00		
5-9.9	0.95	0.83-1.08	0.4032
10-14.9	0.87	0.72-1.04	0.1312
15-19.9	0.98	0.74-1.29	0.8726
≧20	1.00	0.65-1.54	0.9918
Average daily sunshine hours			
0-2.49 hrs	1.03	0.92-1.15	0.5776
2.50-4.99	1.00		
5.00-7.49	1.06	0.94-1.18	0.3519
7.50-9.99	1.01	0.91-1.13	0.8473
≧10	1.13	0.99-1.30	0.0738

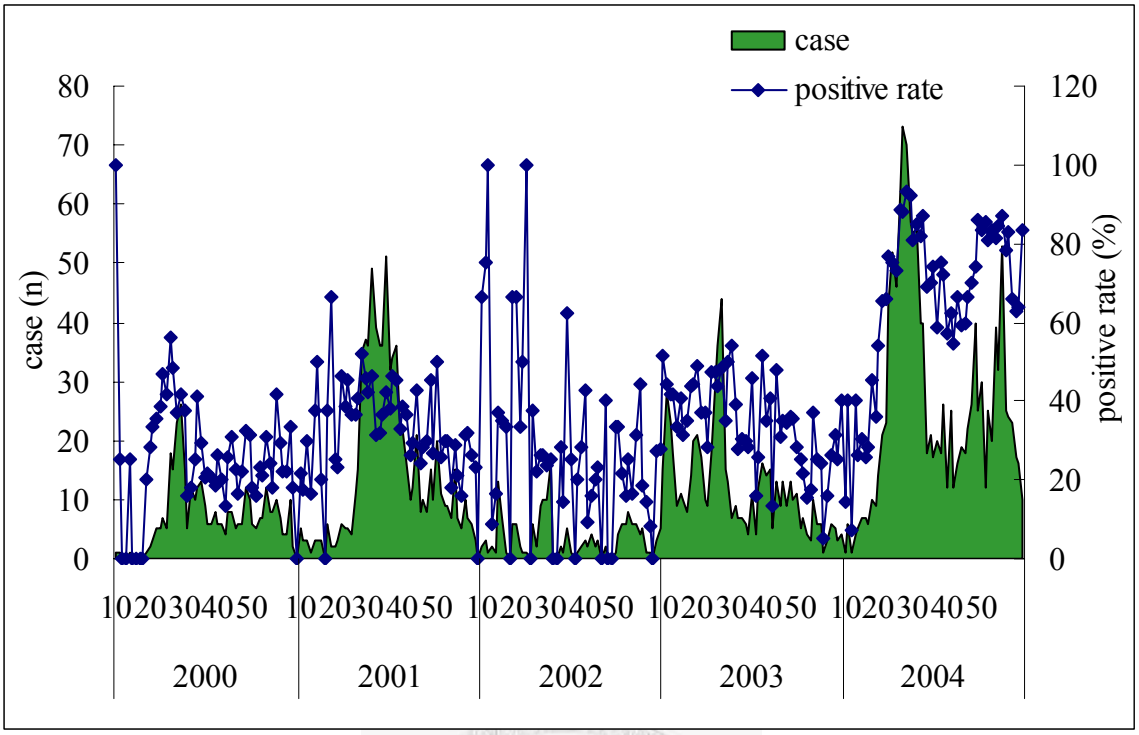


Figure 1 Numbers and rates of enteroviral disease specimens tested positive at laboratories by week in 2000-2004, Taiwan

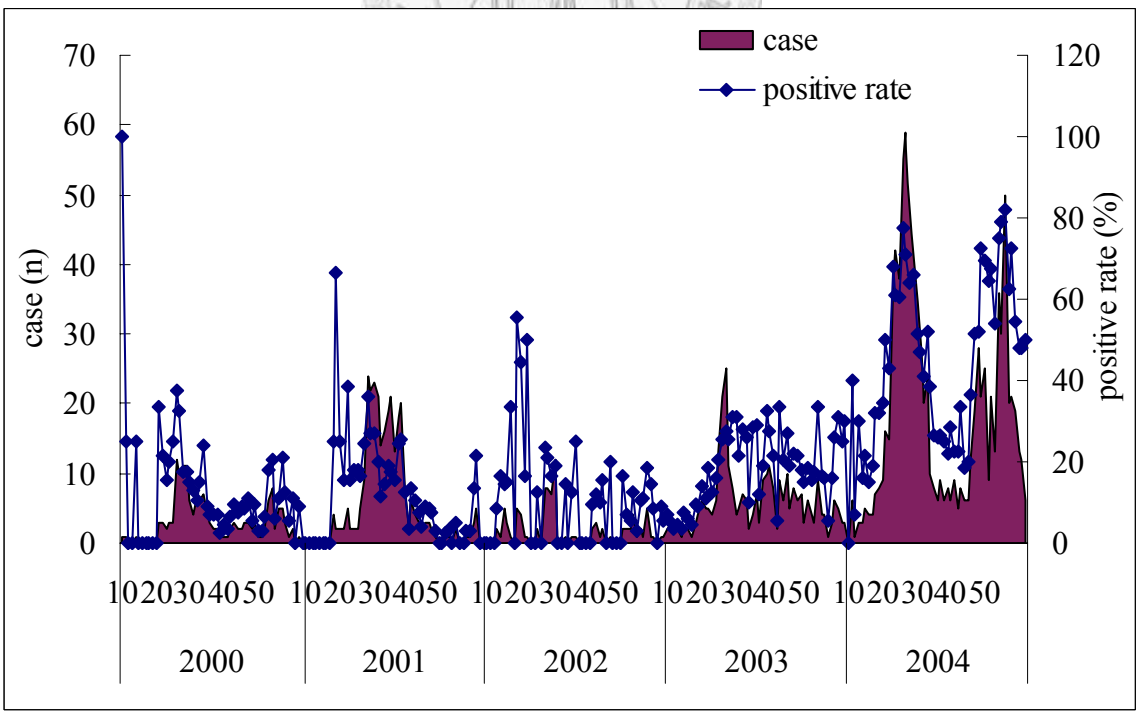


Figure 2 Cases and rates and of pan-enterovirus tested positive at laboratories by week in 2000-2004, Taiwan

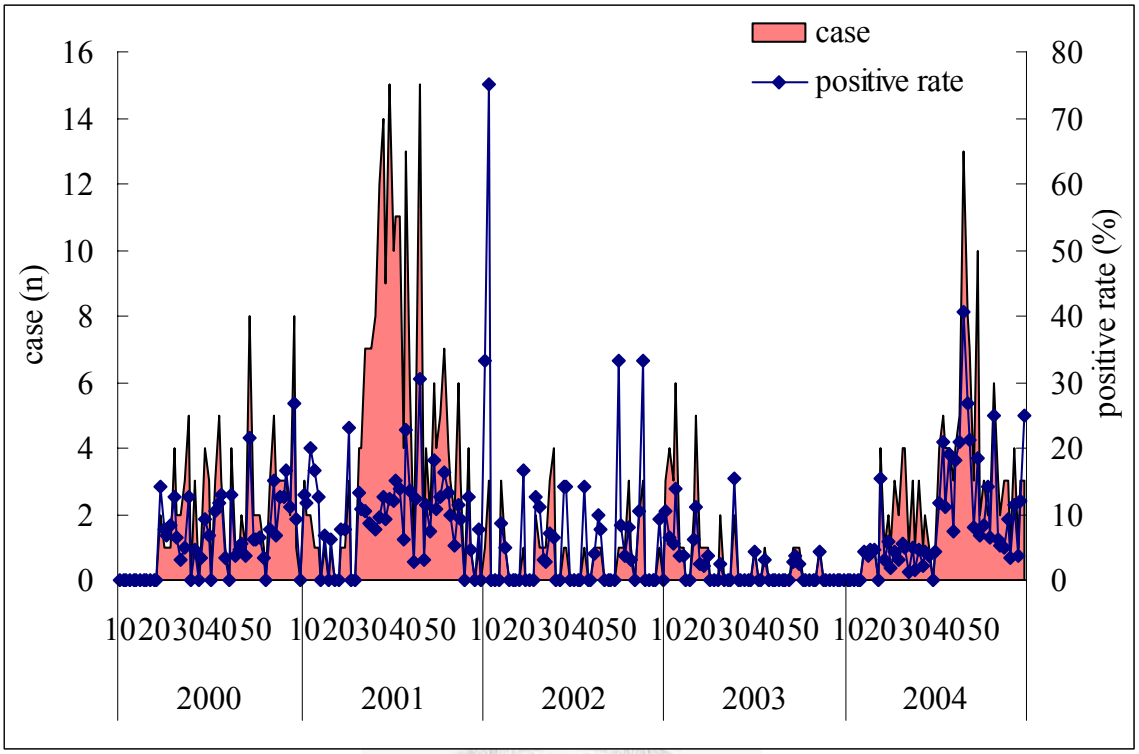


Figure 3 Cases and rates of EV71 tested positive at laboratories by week in 2000-2004, Taiwan

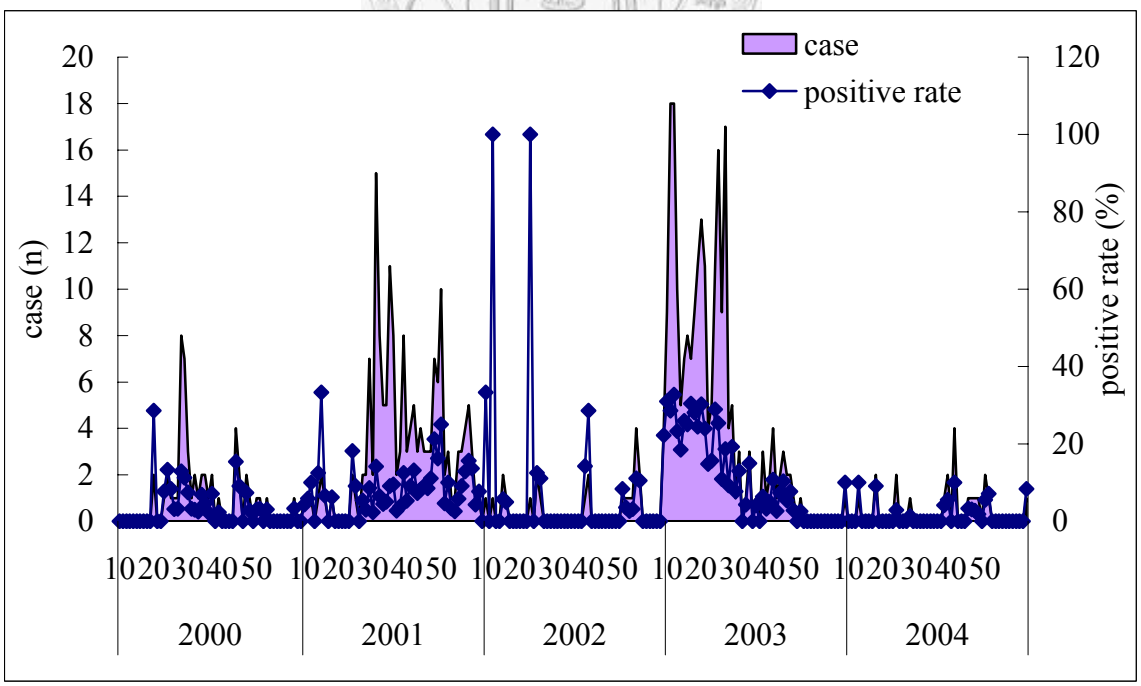


Figure 4 Cases and rates of CA16 tested positive at laboratories by week in 2000-2004, Taiwan

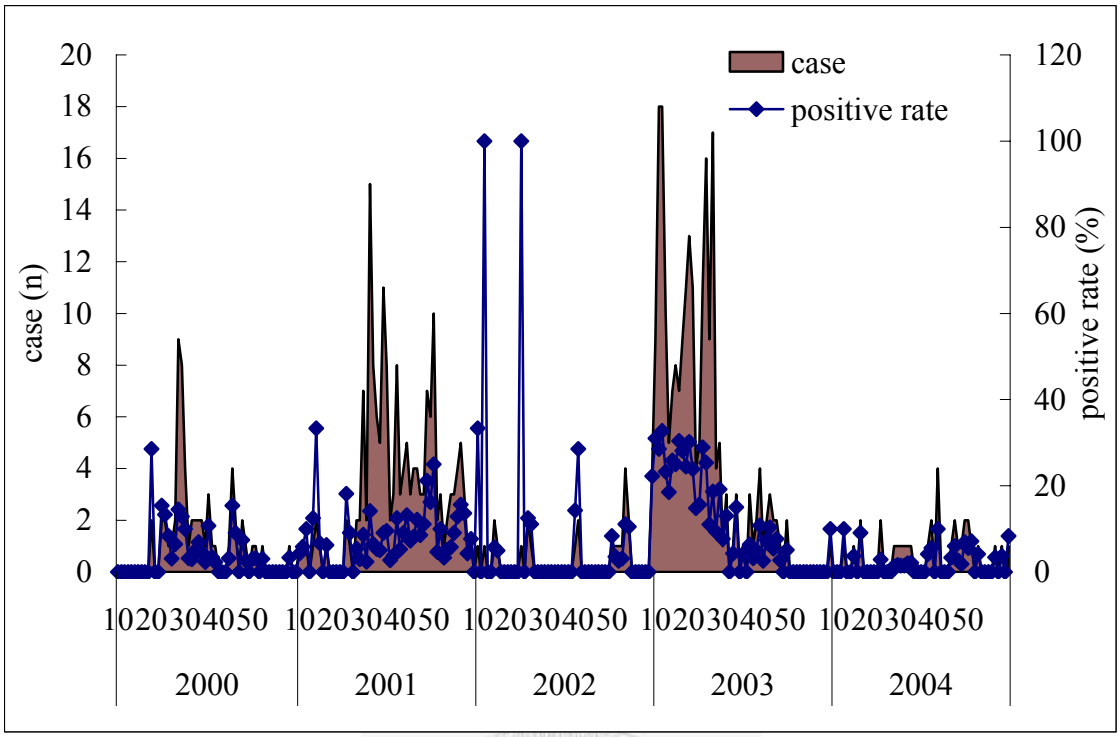


Figure 5 Cases and rates of Coxsackie group A tested positive at laboratories by week in 2000-2004, Taiwan

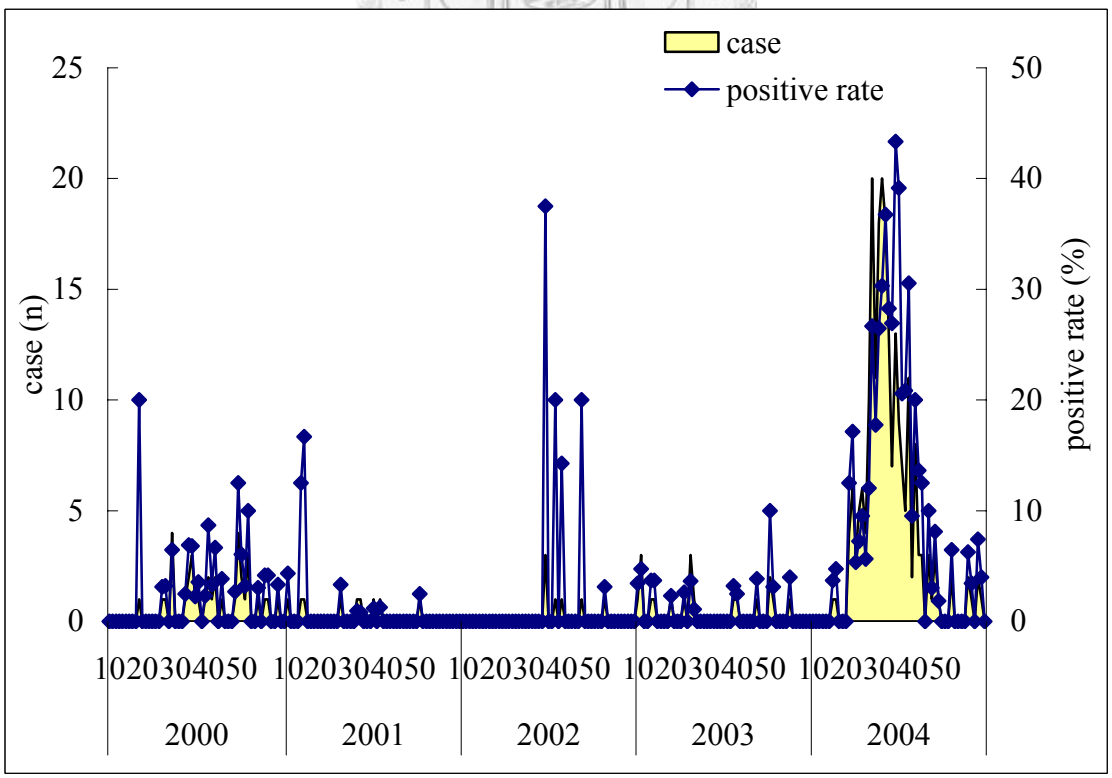


Figure 6 Cases and rates of Coxsackie group B tested positive at laboratories by week in 2000-2004, Taiwan

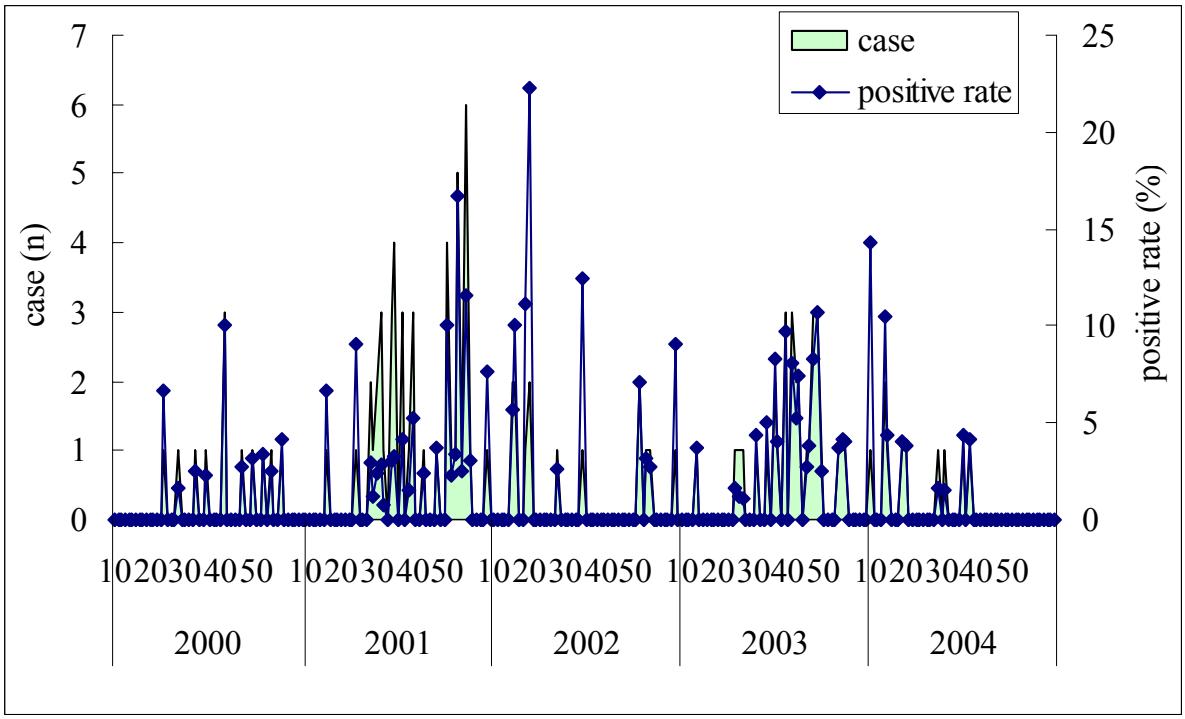
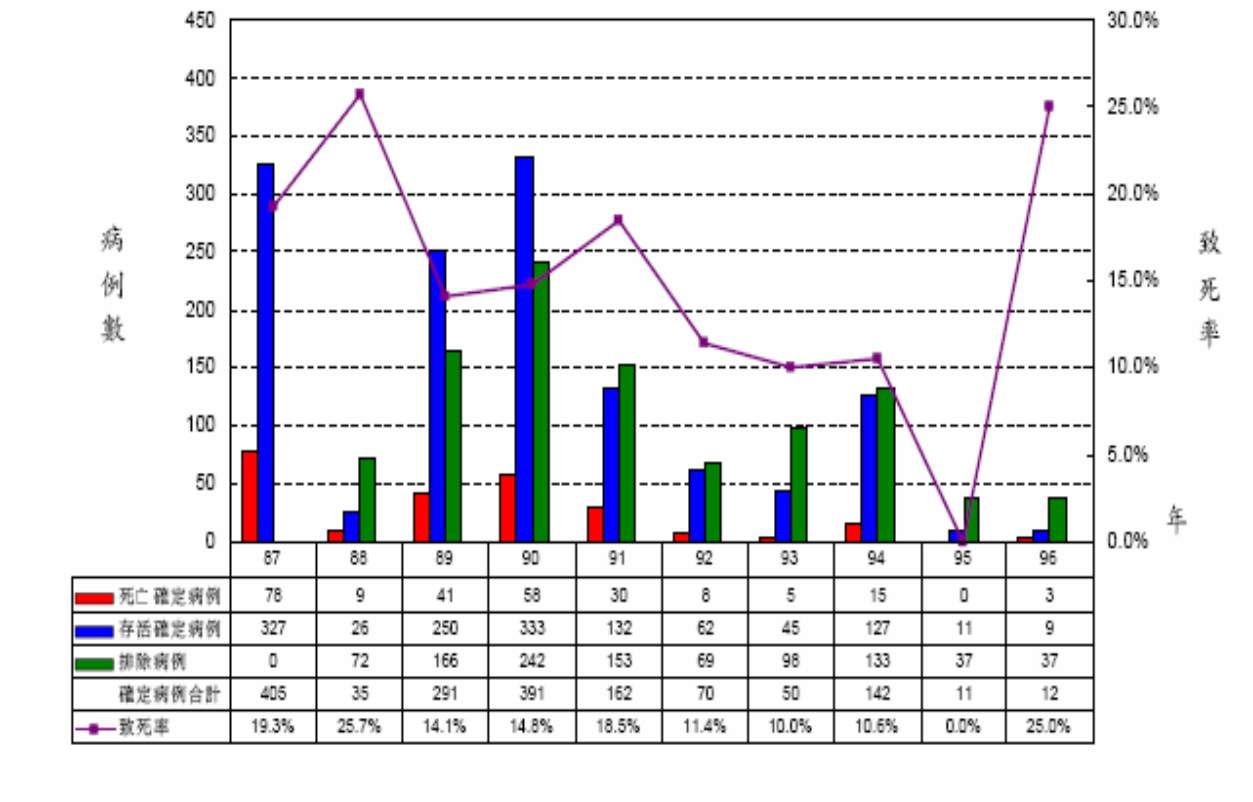


Figure 7 Cases and rates of Echovirus tested positive at laboratories by week in 2000-2004, Taiwan

Appendix 6

CDC information



	87	88	89	90	91	92	93	94	95	96
死亡 確定病例	78	9	41	58	30	6	5	15	0	3
存活確定病例	327	26	250	333	132	62	45	127	11	9
排除病例	0	72	166	242	153	69	98	133	37	37
確定病例合計	405	35	291	391	162	70	50	142	11	12
致死率	19.3%	25.7%	14.1%	14.8%	18.5%	11.4%	10.0%	10.6%	0.0%	25.0%

Figure 1 民國 87 至 96 年台灣地區腸病毒感染併發重症疫情 (資料來源:疾病管制局)