

Keywords: dengue fever, dengue hemorrhagic fever, dengue virus, history of chronic diseases, repeated infections

Foreword

Dengue fever (DF) is an acute infectious disease caused by four serotypes of dengue virus, and also an important vector-borne disease. The virus is transmitted to humans through the bites of infected *Aedes aegypti* or *Aedes albopictus* mosquitoes primarily in tropical and sub-tropical regions. The World Health Organization estimates that there may be 50–100 million dengue infections and several hundred thousand cases of dengue hemorrhagic fever (DHF) throughout the world every year [1, 2]. With the impact of global warming, dengue fever outbreaks have spread to previously non-epidemic areas, and more than two thirds of the countries worldwide are threatened by dengue hemorrhagic fever as well [3]. Taiwan is located in the high-risk subtropical region, so that we need to devote more manpower and resources to preventing the spread of the disease.

Before World War II, Taiwan had three extensive dengue epidemics throughout the island in 1915, 1931 and 1942 [4]. Among them, the 1942 epidemic infected five million people with 80% attack rate. No outbreak had been detected for nearly 40 years afterward until a large-scale outbreak at Liuqiu, Pingtung County in 1981 [5]. Since then, Taiwan faced dengue fever outbreaks of different scales every year. In recent years, except a few minor outbreaks in the central and northern regions, most of the dengue fever outbreaks concentrated in Tainan City, Kaohsiung City and Pingtung County. Most recent large-scale outbreak arose in Kaohsiung area in 2002 with a cumulative total of 5,336 confirmed indigenous cases of dengue fever, 241 indigenous cases of DHF, and 19 cases of death [6]. As the southern region is a high-risk area for dengue fever infection, and four serotypes of dengue virus have presented there, repeated infections with different serotypes of dengue virus may lead to the development of severe DHF. In addition, the indigenous DHF outbreaks in Taiwan seem to have increased year by year recently, bringing great challenges for epidemic prevention.

This study used the data of confirmed indigenous DHF cases from 2003 to 2011 in Taiwan to analyze the correlation between dengue hemorrhagic fever and variables of gender, age, serotype of dengue virus, repeated infection, and chronic diseases in order to provide a reference for epidemic prevention against dengue fever and dengue hemorrhagic fever.

Materials and Methods

A. The research period and objects:

The objects were the cases with onset dates from January 1, 2003 to December 31, 2011, and confirmed as indigenous dengue hemorrhagic fever.

B. The case definition of dengue hemorrhagic fever and clinical criteria [7]:

a. Case definition

The cases meet clinical criteria.

b. Clinical criteria

The following four are required to be met:

1. Fever
2. Bleeding: Meet one or more of the following:
 - (1) Blood pressure cuff test positive
 - (2) Punctate bleeding, petechiae, or purpura
 - (3) Mucous membranes, gastrointestinal tract, intravenous injection site or elsewhere bleeding
 - (4) Bloody stools, hematemesis
3. Thrombocytopenia ($\leq 100,000$)
4. Plasma leakage (due to increased microvascular permeability): Meet one or more of the following:
 - (1) Hematocrit rose more than 20%
 - (2) Hematocrit decreased by 20% after infusion therapy
 - (3) Pleural effusion, ascites, or hypoalbuminemia ($\leq 3\text{gm/dl}$)

C. Data sources and analytical methods

We used the epidemiological data from Taiwan CDC's notifiable diseases surveillance system and business objects system to identify the indigenous DHF confirmed cases with onset dates between January 1, 2003 and December 31, 2011, and took the epidemiological investigation system to create the database. Descriptive statistics was used for analysis of the confirmed case number and deaths of dengue hemorrhagic fever, and for analysis of gender, age, residential areas and serotypes of virus. For bivariate statistics, we used chi-square test, Fisher's exact test, and two-sample t test to analyze the correlation between the predictor and outcome variables and calculated whether the value was statistically significant. Demographic data were the mid-year population census data from 2003 to 2011 from the Ministry of the Interior. This study used EXCEL and PASW Statistics 18.0 software to code and analyze. The significance level of all tests was set at $p < 0.05$.

Results

A. Epidemiological analysis of DHF cases in Taiwan from 2003 to 2011

a. The number of confirmed cases and deaths

The annual number of DHF confirmed cases in Taiwan from 2003 to 2011 was 20 cases or less. A total of 93 cases were confirmed in these nine years (Figure 1). The number of cases had slightly increased since 2009, and deaths had occurred for three consecutive years. The average case fatality rate for the nine years was 17.2%. The case numbers of DHF and DF were highly correlated ($R = 0.764$), and the correlation was statistically significant ($p < 0.05$). In the last three years, the serotypes of DHF cases were mostly the predominant serotypes of DF. This suggests that when any serotype of dengue virus was locally current for a while, the dengue epidemic would be more severe and the risk of people being infected with dengue hemorrhagic fever would be higher as well.

b. Gender and age

In the 93 indigenous dengue hemorrhagic fever cases, the male to female ratio was 1.21:1. The average age of the cases was 55 years (SD 21.9, range 1-81). Infected people were mainly young and elderly, especially the 60-69 age group and those older than 70 years old, accounting for 31.2% and 28.0% respectively (Figure 2). The incidence was lowest in the 20-29 age group. It showed an upward trend in those older than 30 years old with the highest incidence of 0.212 per 100,000 population in the 60-69 age group which were 5 to 35 times higher compared with people under 60 years old. Females were the majority in 30-59 year-old cases, while men were mainly in the elderly above 60 years old. However, the male to female ratio was statistically significant ($p < 0.05$) only in cases over 70 years old.

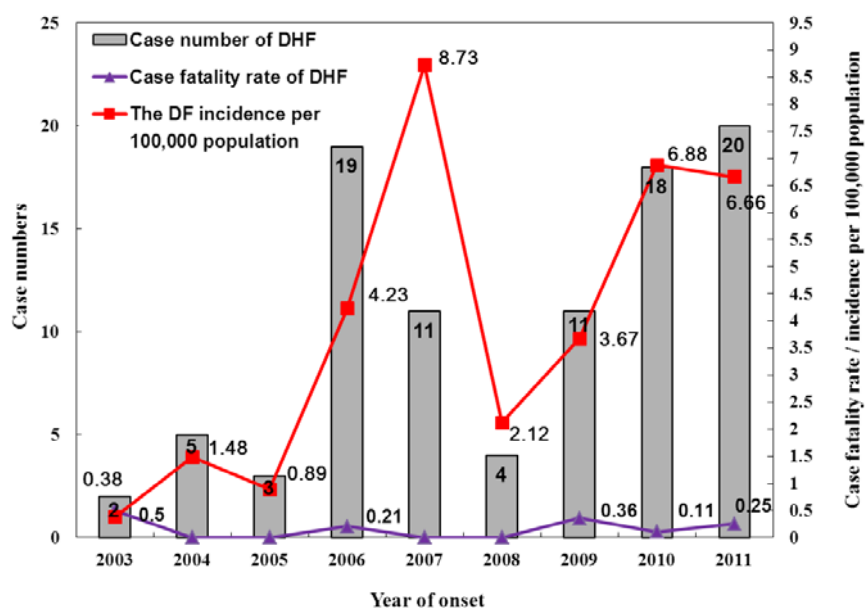


Figure 1. DHF epidemic trends in Taiwan from 2003 to 2011

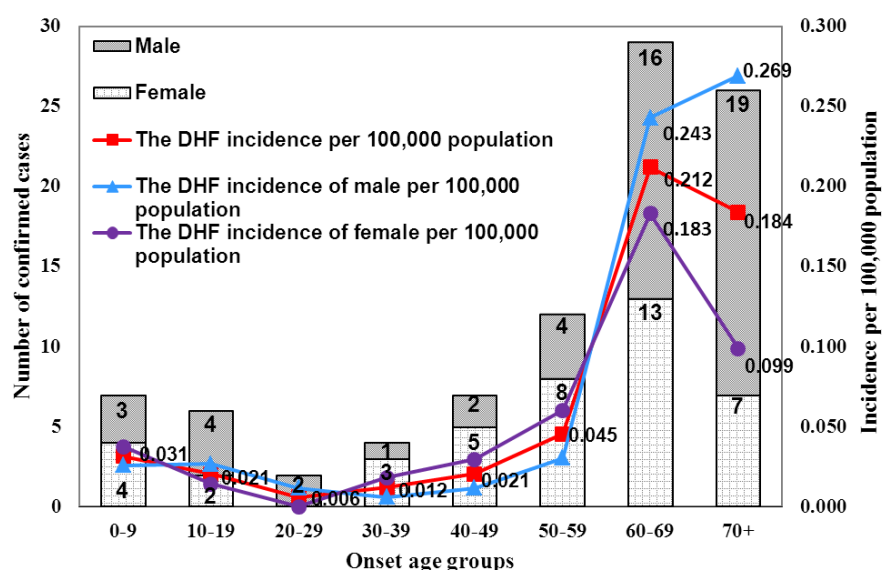


Figure 2. The incidence trends of DHF cases in Taiwan by age and gender from 2003 to 2011

c. Residential areas and the serotypes of dengue virus

The indigenous DHF cases were mainly acquired in Tainan City, Kaohsiung City and Pingtung County (Table 1) with the highest of 62 cases in Kaohsiung City. The majority of virus serotypes among DHF cases in the nine years, except the untyped virus strains, were DEN-2 (40.9%) and DEN-3 (36.4%). As imported virus strains had differences, the dengue virus detected in Tainan City was completely different from the virus detected in Kaohsiung City. Statistical analysis also showed significant difference ($p < 0.001$) among various counties and cities regarding the serotypes of current dengue virus.

Table 1. The virus serotypes and residential areas of DHF cases in Taiwan from 2003 to 2011

DHF cases	Serotypes of dengue virus (n=44)					χ^2 (p^a)
	DEN-1	DEN-2	DEN-3	DEN-4	Total	
Residential area						36.29 (<0.001)
Tainan City	7	0	0	2	9 (20.5%)	
Kaohsiung City	0	17	15	0	32 (72.7%)	
Pingtung County	1	1	1	0	3 (6.8%)	
Total	8(18.2%)	18(40.9%)	16(36.4%)	2 (4.5%)	44(100.0%)	

Note: ^a p value (excluding untyped virus)

Case number with untyped virus: 15 in Tainan City, 30 in Kaohsiung City, 4 in Pingtung County

B. Serotypes of DHF virus and infected groups in Taiwan from 2003 to 2011

a. The virus serotypes of DHF cases

In the 93 indigenous DHF cases, 16 (17.2%) stated that they had been infected with dengue fever. Of which, 50.1% was elderly over 60 years old. More than 65% of the confirmed DHF cases lived in Kaohsiung City. Except untyped virus, DEN-2 virus was predominant in cases with histories of dengue fever infections. In 54 cases (58.1%) of first time infection with dengue fever, DEN-3 virus was predominant when excluding untyped virus. Dengue fever infection history had statistically significant correlation with age ($p < 0.01$). Of the 0-69 age group, it showed that the older of age, the higher the proportion of repeat dengue fever infections (Table 2).

b. The elderly over 60 years old and those with chronic diseases

With age rising, the number of cases with chronic diseases was also increasing. Of the cases with chronic diseases, 14 (41.2%) were 60-69 years old and 11 (32.4%) were over 70 years old. In the 60-69 age group, 48.3% had chronic diseases, while in elderly over 70 years old, the proportion was 42.3%. The results showed in Table 2 that age had statistically significant correlation with chronic diseases ($p < 0.01$).

Among the 93 DHF cases, 34 (36.6%) were with chronic diseases, 29 had no history of chronic diseases, and the remaining 30 cases' records were unavailable. For the 34 cases with chronic diseases, 21 of them (61.8%) had multiple chronic diseases which were mainly hypertension (20 cases) and diabetes (13 cases), accounting for 58.8% and 38.2% respectively.

Table 2. The DF infection histories and chronic diseases among DHF cases in Taiwan from 2003 to 2011

DHF cases	Infection history of DF			χ^2 (p^a)	Chronic disease			χ^2 (p^a)
	Yes (n=16)	No (n=54)	Unknown (n=23)		Yes (n=34)	No (n=29)	Unknown (n=30)	
Gender				0.46 (0.50)				1.96 (0.16)
Male	7 (43.8%)	31 (57.4%)	13 (56.5%)		20(58.8%)	11 (37.9%)	20 (66.7%)	
Female	9 (56.3%)	23 (42.6%)	10 (43.5%)		14(41.2%)	18 (62.1%)	10 (33.3%)	
Age				17.56 (<0.01)				18.67 (<0.001)
0-39	1 (6.3%)	12 (22.2%)	6 (26.1%)		1 (2.9%)	12 (41.4%)	6 (20.0%)	
40-49	2 (12.5%)	2 (3.7%)	3 (13.0%)		4 (11.8%)	1 (3.4%)	2 (6.7%)	
50-59	5 (31.3%)	3 (5.6%)	4 (17.4%)		4 (11.8%)	4 (13.8%)	4 (13.3%)	
60-69	7 (43.8%)	12 (22.2%)	10 (43.5%)		14 (41.2%)	3 (10.3%)	12 (40.0%)	
70+	1 (6.3%)	25 (46.3%)	0 (0.0%)		11 (32.4%)	9 (31.0%)	6 (20.0%)	
Virus Serotype				3.45 (0.34)				
DEN-1	0 (0.0%)	5 (9.3%)	3 (13.0%)					
DEN-2	6 (37.5%)	8 (14.8%)	4 (17.4%)					
DEN-3	4 (25.0%)	10 (18.5%)	2 (8.7%)					
DEN-4	0 (0.0%)	2 (3.7%)	0 (0.0%)					
Untyped	6 (37.5%)	29 (53.7%)	14 (60.9%)					

Note: ^a p value (excluding unknown histories and untyped virus)

C. The deaths and survival analysis of DHF confirmed cases in Taiwan from 2003 to 2011

Table 3 illustrates both the deaths and survival indigenous DHF cases in Taiwan from 2003 to 2011. In the fatal cases, the male to female ratio was 1.67:1, and the average age was 66.1 years old (SD 11.2, range 40-81). The deaths increased with age. The mortality rate in males was higher than females. The average age of the deaths was about 13 years significantly higher than the average age of survival cases ($p < 0.05$).

As for the serotypes of dengue virus, five (31.3%) and four (25.0%) of the deaths were infected by DEN-3 and DEN-2 respectively. The four serotypes of dengue virus each affected at least one survival case, mostly DEN-2 (14 cases) and DEN-3 (11 cases). The majority of deaths and survival cases were both without DF infection histories, accounting for 8 cases (50.0%) and 46 cases (59.7%) respectively. There were four cases (25.0%) with DF infection histories among deaths and 12 (15.6%) in survival cases.

As for chronic diseases, 12 cases (75.0%) had chronic diseases in the 16 deaths, mainly hypertension (8 cases, 50.0%) and diabetes (7 cases, 43.8%). In the 77 survival cases, 22 (28.6%) had chronic diseases, with mostly hypertension and diabetes as well. Chronic diseases had statistically significant correlation with the living status of DF infected cases ($p < 0.01$). To further analyze the chronic diseases, Table 4 shows that the living status of DF infected cases were significantly correlated with hypertension ($p < 0.05$), diabetes ($p < 0.01$) and heart diseases ($p < 0.05$). Also, the risk of death among the cases with heart diseases was 14.7 times higher than those without heart diseases. And the risk of death among the cases with hypertension and diabetes were 5.1 times and 8.6 times higher compared to those

without these diseases. For the cases with multiple chronic diseases, the risk of death was as high as 15.1 times than non-chronic cases or those with unknown histories of chronic diseases.

Table 3. The death and survival of DHF cases in Taiwan from 2003 to 2011

DHF cases	Living Status		χ^2 (p^a)
	Death (n=16)	Survival (n=77)	
Gender			0.16 (0.69)
Male	10 (62.5%)	41 (53.2%)	
Female	6 (37.5%)	36 (46.8%)	
Age			2.27 (<0.05)
Average age \pm SD ^b	66.1 \pm 11.2	52.7 \pm 22.9	
Age group			7.31 (0.09)
0-39	0 (0.0%)	19 (24.7%)	
40-49	2 (12.5%)	5 (6.5%)	
50-59	2 (12.5%)	10 (13.0%)	
60-69	5 (31.3%)	24 (31.2%)	
70+	7 (43.8%)	19 (24.7%)	
Virus serotype			3.23 (0.33)
DEN-1	0 (0.0%)	8 (10.4%)	
DEN-2	4 (25.0%)	14 (18.2%)	
DEN-3	5 (31.3%)	11 (14.3%)	
DEN-4	0 (0.0%)	2 (2.6%)	
Untyped	7 (43.8%)	42 (54.5%)	
DF infection history			0.33 (0.57)
Yes	4 (25.0%)	12 (15.6%)	
No	8 (50.0%)	46 (59.7%)	
Unknown	4 (25.0%)	19 (24.7%)	
Chronic disease			7.85 (<0.01)
Yes	12 (75.0%)	22 (28.6%)	
No	1 (6.2%)	28 (36.4%)	
Unknown	3 (18.8%)	27 (35.1%)	

Note: ^a p value (excluding unknown histories)

^b Using the t-test to analyze the association between the average age and death

Table 4. The types of chronic diseases and living status among the DHF cases in Taiwan from 2003 to 2011

DHF cases	Living Status		P
	Death (n=16)	Survival (n=77)	
Chronic disease (have/none)			
Hypertension	8 (40.0%)	12 (60.0%)	<0.05
Diabetes	7 (53.8%)	6 (46.2%)	<0.01
Heart diseases	3 (75.0%)	1 (25.0%)	<0.05
Renal diseases	2 (66.7%)	1 (33.3%)	0.085
Liver diseases	2 (50.0%)	2 (50.0%)	0.162
Lung diseases	2 (66.7%)	1 (33.3%)	0.085
Arthritis & Gout	2 (66.7%)	1 (33.3%)	0.085
Gastrointestinal diseases	1 (25.0%)	3 (75.0%)	0.824
Multiple chronic diseases ^a	11 (52.4%)	10 (47.6%)	<0.001

Note: ^a The multiple chronic diseases were defined as the cases with two or more chronic diseases

Discussion and recommendations

A. The distribution of DHF cases in Taiwan

To review the trends of dengue fever transmission in Taiwan in recent years, we found the pattern gradually developed into one where the dengue virus was usually imported from Southeast Asia in early summer and was then spread during fall by vector mosquitoes, mainly distributed in southern Taiwan. In the cold winter, the vector mosquitoes became less active, and the epidemic of dengue fever gradually subsided [1, 8]. There were 8,062 indigenous cases of dengue fever and 93 indigenous cases of dengue hemorrhagic fever reported in Taiwan from 2003 to 2011. The DHF cases accounted for about 1% of DF infection, however, the patients infected with DHF would develop symptoms as plasma leakage, body edema and abnormal bleeding after the fever relieved. In some severe cases, DHF would even lead to dengue shock syndrome. The case fatal rate may exceed 20% without immediately appropriate treatment, but it can be reduced to 1% under rapid diagnosis and proper treatment [9].

With rapid reporting and diagnosis as well as appropriate medical treatments in recent years, the case fatal rates of DHF in most DF endemic countries have decreased [10]. Currently, the case fatal rates in Southeast Asian and South American countries are between 1% to 5% [11, 12]. The case fatal rate of indigenous DHF cases was 17.2% on average in Taiwan from 2003 to 2011. For repeated infections, the case fatal rate can be as high as 25%. The obviously higher risk of death in Taiwan compared to other DF endemic countries may be due to the fact that dengue fever outbreaks in Taiwan were mostly subsequent to imported cases. Unlike the majority of cases of DF endemics in Southeast Asian countries, who are children, the DHF cases in Taiwan are mostly the elderly with higher risk of repeated infections. The elderly are prone to have various chronic diseases as their immune function decreased. Since only supportive therapy is available for now, when they are infected with dengue hemorrhagic fever, it can easily lead to death. In addition, the annual number of confirmed DHF cases during this study was less than 20 cases, making the overall case fatality rate rather high. No matter the high case fatality rate of DHF cases in Taiwan was caused by old age of cases or other factors not yet identified, it is a fact that DHF is relatively easier to cause the death than DF.

B. The serotypes of DHF cases in Taiwan

Most cases of dengue hemorrhagic fever are repeated infections with a different serotype of dengue virus from the first infection, causing virus antibody cross-reaction [3]. Alternatively, they can also result when dengue virus strains continue to circulate in the same geographic region [13]. This is because different pathogenic or different virus strains cross-infect different hosts in the same area over a long period of time, resulting in viral gene mutation into stronger virulence and more easily leading to serious illness. The sub-typed virus of DHF cases in this study was primary DEN-2. The repeated infections accounted for 17.2% DHF cases, wherein the DEN-2 virus was also predominant. This result was

consistent with the studies by Lin et al. and Yeh et al. [1, 3]. In this study, first time infections accounted for 58.1% of the DHF cases, and mostly by DEN-3 virus. This result was similar with the report from Anantapreecha et al. [14] which suggested that a small number of cases developed DHF during first infection with DEN-1 or DEN-3 virus.

For those who had subsequent infections by DEN-2 virus, the severity of DHF would depend on the virus serotype in their first infection. First infection with DEN-1 virus would cause the severest symptoms, followed by DEN-3 virus, and DEN-4 virus was mildest [15]. Lin et al. [1] suggested that repeated DF infections would increase the risk of developing DHF, but wouldn't increase the mortality. This is consistent with the findings in this report. Another study by Guzman et al. mentioned that DHF could still happen even with a long interval between first and subsequent infections [16]. In this study, we found some DHF cases were actually re-infected with dengue virus more than 20 years after their first infection. Individuals who have been infected with dengue fever, no matter how long from the previous infection, should avoid re-infection which can cause severe illness.

Only 17.2% of the DHF confirmed cases in this study had repeated infections based on their self-statements. However, according to the program of science and technology research and development from 2005 to 2007 by Taiwan CDC [17-19], the serologic prevalence of dengue fever in citizens over the age of 65 in some townships of Kaohsiung City, Pingtung County and Tainan City was about 30-90%, and the secondary infection rate was about 30-70%. This suggests that the actual repeated infection rate of DHF confirmed cases should be higher than this study found. It was probably due to the fact that most cases were asymptomatic in first infections, and the lack of surveillance data and medical records for former cases can also lead to an underestimation of the repeated infection rate of DHF confirmed cases. Some literatures mentioned that repeated infections of DEN-2 virus were prone to developing DHF [1, 3, 14]. In this study, we found DEN-2 virus was predominant in repeated infection cases in Taiwan from 2003 to 2011. Nevertheless, further research is needed to verify whether repeated infections of DEN-2 virus were indeed prone to developing DHF or whether the predominance of the DEN-2 virus in recent years has made this virus strain the main source of DHF cases.

C. The susceptible groups of dengue hemorrhagic fever in Taiwan

In analysis of DHF cases in Taiwan from 2003 to 2011, the susceptible groups with high proportion of infection were as follows:

a. The elderly over 60 years old

In view of international epidemic information, children under 15 years of age and the elderly were more susceptible to dengue hemorrhagic fever and prone to death [13, 15]. The indigenous DHF confirmed cases in Taiwan were mainly the elderly aged over 60 years. It was obviously different from endemic areas of Southeast Asia where the primarily susceptible group was children [14, 20]. The study by Lee et al. [13] noted that

elderly over 60 years old infected with dengue fever were more susceptible to developing dengue hemorrhagic fever than young people, and had higher risk of death after infection. The average age of DHF deaths in Taiwan from 2003 to 2011 was 66.1 years old which was 13 years higher than the survivors. The higher case fatality rate in the elderly was consistent with the literature found. The study results showed that male DHF cases over 70 years old were significantly more than female cases in Taiwan for the recent nine years. There was no statistical gender difference in the remaining age groups. This result might be related to limited cases of all ages. As for whether the gender differences were associated with DHF infection, further studies are needed.

b. People with chronic diseases

Among DHF cases in the last nine years, more than one third (34 cases) had chronic diseases, mainly were hypertension and diabetes. Some literatures mentioned that people with chronic diseases such as hypertension, diabetes, asthma, and heart diseases were more likely to be infected with dengue hemorrhagic fever [12]. In addition, the study by Pang et al. [21] showed that Chinese people with diabetes and hypertension had a risk of DHF infection that was 2.1 times higher than those without chronic diseases. Our study also found that the majority of DHF cases were people with chronic diseases, and most of them were the elderly. According to the national health survey in 2009 conducted by the Bureau of Health, about 86.2% of the elderly had been diagnosed with at least one chronic disease, and 66.1% had been diagnosed with at least two chronic diseases. The prevalence of chronic diseases (45.5%) among DHF cases over 60 years old in this report was lower than the findings by the Bureau of Health, probably an underestimation due to unavailable records of chronic diseases for 18 cases. After excluding the cases with unknown chronic records, the proportion of the elderly over 60 years old with chronic diseases to all cases with chronic diseases (25/34) was 1.8 times higher than the proportion of the elderly over 60 years old without chronic diseases to all cases without chronic diseases (12/29). If the cases with unknown chronic records were all without chronic diseases, the proportion was still 1.4 times higher. Therefore, the elderly with chronic diseases were found to be more susceptible to infection with dengue hemorrhagic fever even when underestimated.

As for whether chronic disease patients had higher fatality rate of DHF infection, up to 75% of the deaths in this study had chronic diseases, and the cases with heart diseases, diabetes and hypertension were more likely to die. This result was similar with the conclusion of the research by Liu et al. [22] which suggested DHF cases with hypertension, chronic renal failure or diabetes were associated with high case fatality. This shows that chronic disease patients were not only susceptible to dengue hemorrhagic fever, but also had higher case fatality rate. Therefore, patients with chronic diseases in Taiwan should be more vigilant in preventing dengue hemorrhagic fever in order to reduce the risk of death.

D. Recommendations

As the DF vector mosquitoes distribution areas expand, people should be thorough in eliminating breeding sources and take self-protection measures. Meanwhile, border quarantine should be strengthened to avoid local transmission via imported dengue virus. Although the incidence of dengue hemorrhagic fever in Taiwan is not high, the average case fatality rate in recent years was as high as 17.2%. Consequently, we provide the following recommendations as a reference for epidemic prevention and control:

a. To increase physicians' awareness and capacity of diagnosis and treatment

Many DF cases have atypical early symptoms, and are diagnosed as the common cold. We recommend that local health authorities maintain close contact with local hospitals through visits or by disseminating relevant information through local medical associations before the start of each dengue season, in order to enhance clinicians' awareness. Furthermore, as the progression of dengue hemorrhagic fever is particular, we suggest continuously conducting educational training, seminars or online digital learning courses on DHF diagnosis and treatment, to enhance clinicians' abilities of diagnosis and treatment and to reduce the occurrence of DHF deaths.

b. To strengthen the health education for chronic disease patients and cases who have been infected by dengue virus in high-risk counties and cities

With global climate change and frequent international interaction, the threat of locally-acquired DF induced by imported cases has largely increased. When chronic disease patients are infected with dengue virus, their risk of developing DHF and death will increase. It is advisable to strengthen the health education for chronic disease patients and those who has been infected by dengue virus in order to enhance public knowledge of epidemic prevention, particularly in high risk administrative areas. Physicians or outbreak investigators are advised to educate the DF confirmed cases to be vigilant and take self-protection measures since re-infection with dengue virus will increase the probability of developing severe dengue hemorrhagic fever.

Limitations

The main limitation of this study was the difficulty in virus sub-typing in some of the DHF cases when taking samples at reporting. Also, the medical histories of dengue fever infection or chronic diseases were based on cases' self-statements recorded from the epidemiological investigation system without laboratory or medical confirmation.

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Analysis of Intravenous Peramivir for Treatment of Seasonal Influenza Infections, Taiwan, 2010-2012

Hsiao-Yun Tsai¹, Mei-Ling Lin¹, Yi-Chien Chih¹, Shu-Mei Chou¹,
Chang-Hsun Chen², Chin-Hui Yang¹

1. Division of Preparedness and Emerging Infectious Diseases, Centers for Disease Control, Ministry of Health and Welfare, Taiwan
2. Division of HIV/AIDS and TB, Centers for Disease Control, Ministry of Health and Welfare, Taiwan

Abstract

Peramivir is a newly developed intravenous administrated neuraminidase inhibitor used to treat influenza, effective against both influenza A and influenza B infections. It is not approved in Taiwan yet, so a patient's or family's consent is required before administration. Taiwan Centers for Disease Control (Taiwan CDC) started to import peramivir from Japan under special permit since 2010. Oral and inhaled antivirals, Tamiflu (oseltamivir) and Relenza (zanamivir) in respective, are the first choices of treatment in influenza patients qualified for government-funded antivirals. Peramivir was imported to treat patients who cannot take Tamiflu orally or inhale Relenza due to unconsciousness or other morbidities, and to build a diverse stockpile of antivirals for our country. Because only physicians can prescribe intravenous injection and the price of the drug is high, peramivir is only used in qualified patients with severe complicated influenza. In this article, we analyzed 68 patients who had been treated with peramivir during 2010-2011 or 2011-2012 influenza seasons after obtaining permission from the district commander of the Communicable Disease Control Medical Network. Four hundred and thirty-nine packs were used. Compared with the number of patients with confirmed complicated influenza infection in two flu seasons, 1,784 in 2010-2011 and 1,704 in 2011-2012, and the number of death, 140 and 154 deaths in respective, the number of patients using peramivir was relatively small. More education on primary care physicians about the timing of peramivir usage is needed, because it is the only alternative in severe patients who cannot take orally or inhale other medications.

Keywords: peramivir, antivirals, severe complicated influenza

Introduction

Peramivir, like oseltamivir (Tamiflu), and zanamivir (Relenza), is a neuraminidase inhibitor used for treating influenza, and is effective against both influenza A and influenza B infections. The aforementioned three drugs have different administration routes, but all can be used in treating patients with influenza infection. Tamiflu is an orally administrated

capsule, Relenza is an inhaled dry powder, and peramivir is an intravenous injection drug [1-2]. Peramivir is better in the affinity to influenza virus and in the serum drug clearance rate. It is recommended to use once daily, and can be stopped when the clinical condition improves [3]. Currently most countries do not stockpile peramivir because it is only approved in Japan and Korea now, and it has just passed the phase III clinical trial in United States. During 2009 H1N1 pandemic, Food and Drug Administration of the United States had provisionally approved the use of peramivir in hospitalized influenza patients based on the regulations of Emergency Use Authorization [4]. The drug, known as Rapiacta[®], was then approved by Ministry of Health, Labour, and Welfare of Japan in January 2010. Two different sizes of packages are commercially available, 15 ml liquid containing 150mg peramivir in a vial and 60 ml liquid containing 300 mg drug compound in a bag.

To treat patients with complicated influenza infection who are unable to take Tamiflu orally or inhale Relenza because of poor consciousness or other morbidities, intravenous peramivir is an alternative currently available on the market, with government approval. Taiwan CDC started to import peramivir from Japan under special permit since 2010, so that a diverse stockpile of antivirals can be built. Peramivir is allocated in branches of Taiwan CDC, as well as local health bureaus of remote islands such as Lienchiang, Kinmen, and Penghu Counties. Criteria used to identify a patient qualified for government-funded antivirals were announced. Doctors should consider use of peramivir in those qualified but not able to use oral or inhaled antivirals due to coma or other complications. Application to local branch of Taiwan CDC, permission from the district commander of the Communicable Disease Control Medical Network, and a family's consent are needed before administration of peramivir.

In this article, we reviewed the 68 patients who had been treated with peramivir during 2010-2011 or 2011-2012 influenza seasons after obtaining permission from the district commander of the Communicable Disease Control Medical Network. Four hundred and thirty-nine packs were used. Age, gender, total used dose of peramivir, and patient's identification were analyzed. The results would be useful in helping establish plans for purchase and storage of antivirals in the future.

Materials and Methods

1. Indication, dosage and administration of peramivir

Each bag of Rapiacta[®] contains 300 mg peramivir and should be given via intravenous infusion. The standard adult dose is 300 mg once daily administrated intravenously for at least 15 minutes. For those with complications and severe cases, intravenous administration of 600 mg once daily with an infusion time more than 15 minutes is recommended. Repetitive use should be considered in patients with persistent symptoms. Dosage should be adjusted according to the age and severity of a patient. The standard dose for children is 10 mg/kg once daily given intravenously for at least 15 minutes. Repetitive

administration could be considered in severe cases and the daily maximum dose is 600 mg. Current evidence only supports the effects of peramivir given within 48 hours of influenza symptom onset, so administration as early as possible is recommended. The clinical outcomes on repetitive use and on initiation of treatment after 48 hours of symptom onset are limited. When repetitive administration is considered, symptoms such as fever should be close monitored to decide whether to prescribe the second course of treatment. The serum concentration of peramivir in patients with impaired renal function could be higher than therapeutic level that might last for a long time, so the dosage should be carefully adjusted according to the serum creatinine clearance (CCr). But there is no consensus on how to adjust the dosage in pediatric patients with impaired renal function. Peramivir is indicated in influenza A and B infection, but it is not effective in treatment of influenza C. Prescription of peramivir should be particularly cautious, considering that not every patient acquired influenza A or B infection needs antivirals treatment and the inconvenience of intravenous administration route compared with other oral or inhaled drugs. Common side effects of peramivir, including diarrhea, neutropenia, etc., should be monitored closely so that doctors can stop using the drug and manage the complications in time.

2. Definition of complicated influenza infection

- (1) Clinical criteria: Presence of influenza like illness in a patient who die or need hospitalization or stay in emergent department because of complications such as respiratory or neurological problems, invasive bacterial infection, myocarditis or pericarditis within four weeks of symptom onset.
- (2) Laboratory criteria: Presence of any one of the following criteria.
 - a. Influenza virus isolated from respiratory tract specimen, such as throat swab
 - b. Positive nucleic acid test of clinical specimen
 - c. Positive antigen test of clinical specimen
 - d. Positive serum antibody test, with 4 times of increase in serum anti-influenza antibody titer in recovery phase, compared with the titer in acute phase.
- (3) Epidemiological criteria: History of close contact with laboratory confirmed cases, including taking care or living with patients and direct contact with their respiratory secretions or body fluids.
- (4) Case required to report: Cases that meet clinical criteria.
- (5) Classifications of reported cases
 - a. Possible cases: Cases that meet clinical criteria.
 - b. Probable cases: Cases that meet both clinical and epidemiological criteria.
 - c. Confirmed case: Cases that meet clinical and laboratory criteria, can be sub-classified into the following three groups.
 - (a) No need for intensive care
 - (b) Need intensive care within 14 days of symptoms onset
 - (c) Mortality case

3. Study samples

The study subjects were recruited from patients who had been treated with peramivir during 2010-2011 or 2011-2012 influenza seasons after obtaining permission from the district commander of the Communicable Disease Control Medical Network.

4. Study materials

- (1) Management information system (MIS) of antivirals: We downloaded data of patients treated with peramivir during 2010 and 2011 influenza seasons (July 2010 to June 2011 and July 2011 to June 2012, respectively) from MIS, including patients' characteristics, hospitals, indication of peramivir, and the actual dose that had been used. The serial number of reporting sheet was used to compare and combine the information in MIS and National notifiable disease system.
- (2) National notifiable diseases system: Using the serial number of reporting sheet, we downloaded the data of patients with complicated influenza infection in 2010 influenza season, including patients' demographics, whether or not a confirmed case, and mortality.
- (3) Paper documents recorded by clinicians: We use these to double confirmed the information obtained from MIS system, and use the data regarding treatment duration and treatment dose. Adverse events are required to be reported since January 2012, so additional reporting sheet should be filled if drug adverse event does happen.

5. Statistical analysis

We used Excel to analyze the number of patients and the total dose of peramivir they used. We also described the patients' demographics, including gender, age, resident county or city, and the date peramivir was prescribed.

Results

1. Patients reported to have complicated influenza infection

Between July 2010 and June 2012, a total of 68 patients have used peramivir. Sixty five of them were reported to have complicated influenza infection. Among them 37 were confirmed cases, 17 were probable cases, and 11 were possible cases. Two patients were reported to have influenza like illness but with critical signs. One patient was prescribed with peramivir because of gastric ulcer bleeding which prohibited him from using Tamiflu and Relenza. The outcomes of these patients were summarized in Table 1.

Table 1. Outcomes of patients who used peramivir

Death	Classification of reported cases (%)			Cases not reported or reported but could not be classified (%)	Total (%)
	Confirmed	Probable	Possible		
Yes	25 (68)	6 (35)	3 (27)	0 (0)	34 (50)
No	12 (32)	11 (65)	8 (73)	3 (100)	34 (50)
Total	37 (100)	17 (100)	11 (100)	3 (100)	68 (100)

2. Use of peramivir

Table 2 showed the demographics of the 68 patients who used peramivir between July 2010 to June 2012. Total 439 bags of peramivir have been used, indicating an average of 6 bags used per person per treatment course (minimal 1 bag and maximal 20 bags). The amount of peramivir used peaked in February in both 2010 and 2011 influenza seasons (Figure 1), and the trend was consistent with the influenza epidemic and the incidence of complicated influenza infection. In terms of the treatment dose, 24 patients had doubled dose (600 mg per day), while the rest had 300 mg per day or standard dose adjusted according to body weight or renal function.

The number of patient with complicated influenza infection and death cases were 1,785 and 140 respectively in 2010-2011 influenza season, 1,704 and 154 in 2011-2012 influenza season. One percent of complicated influenza patients in both seasons had used peramivir (23 cases in 2010-2011 and 14 cases in 2011-2012) while about 10% of death patients had been prescribed with the drug.

Table 2. Demographics of the 68 patients who had used peramivir

Variables	N	(%)
Gender		
Male	48	(71)
Female	20	(29)
Age		
0	5	(7)
1-18	15	(22)
19-64	37	(55)
>65	11	(16)
Cities or counties where patients sought medical consultation		
Taipei City	13	(19)
New Taipei City	10	(15)
Taichung City	17	(25)
Changhua County	2	(3)
Tainan City	7	(10)
Kaohsiung City	14	(21)
Hualien County	5	(7)
Influenza season		
2010-2011	41	(60)
2011-2012	27	(40)
Death		
Yes	34	(50)
No	34	(50)

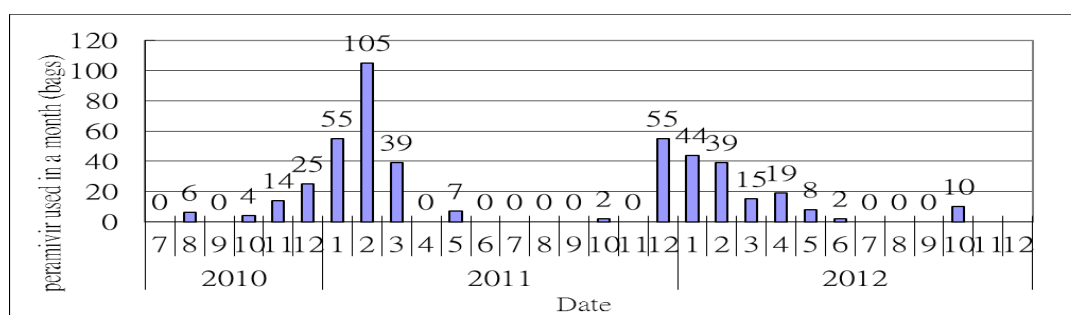


Figure 1. Peramivir used in 2010-2011 and 2011-2012 influenza seasons.

Table 3. Number of patients who had used peramivir in 2010-2011 and 2011-2012 influenza seasons

Influenza season	2010- 2011				2011-2012			
	Confirmed cases (%)	Confirmed case Who died (%)	un-confirmed cases	un-confirmed cases who died	Confirmed cases (%)	Confirmed case who died (%)	un-confirmed cases	un-confirmed cases who died
Used Peramivir	23 (1)	14 (10)	18	6	14 (1)	11 (7)	13	3
Did not use Peramivir	1762 (99)	126 (90)	-	-	1690 (99)	143 (93)	-	-
Total	1785 (100)	140 (100)	-	-	1704 (100)	154 (100)	-	-

Discussion

The mortality rate in patients who used peramivir was 50%. Since full medical records of the deaths and control groups were unavailable, further analysis on clinical benefits of the drug could not be done. But according to studies done in 2009 pandemic H1N1 influenza epidemic in the United States, including surveys on emergency investigational new drug (eIND) between April 2009 - October 23 2009 and between October 23, 2009 - June 23, 2010 [5] and experiences on peramivir emergency use authorization (EUA) [6], the major cause of death in patients who had used peramivir was respiratory failure, other vital organ failure, or complications of pre-existing medical condition of the patient. Based on current available evidence, the drug efficacy in critical patients remained unclear [7].

In this study, we analyzed the 68 influenza patients who had been treated with peramivir in 2010-2011 and 2011-2012 influenza seasons. Total 439 bags of drugs had been used in 23 confirmed cases in 2010-2011 influenza season (14 of them died), and in 14 confirmed cases in 2011-2012 influenza season (11 of them died). Compared with the total case numbers of confirmed complicated influenza infection and death, which were 1,785 and 140 in 2010-2011 influenza season and 1,704 and 154 in 2011-2012 influenza season, not a big proportion of patients had used peramivir. This could be contributed either to the complex application criteria set up by Taiwan CDC (patients should be coma or with other morbidities) or clinicians' unawareness of the using criteria. More education course to inform primary care physicians when and how to use the drug should be arranged in the future. But because the peramivir storage is limited, prescription of the drug should still follow the application criteria.

The number of influenza patients who had used peramivir was more in 2010-2011 influenza season. The first possible explanation was the residual circulating 2009 pandemic H1N1 influenza virus in community, which resulted in more flu patients. The other possible reason was the improvement in peramivir accessibility and the expansion of target populations legitimate for government-funded antivirals in 2011-2012 influenza season.

Most flu patients with minor severity could have been treated with Tamiflu or Relanza earlier in their course, which might decrease the number of critical patients who were more likely to be prescribed with peramivir.

Peramivir is not approved in Taiwan yet, and the price is higher than other antivirals. Considering both the safety and the cost, government-funded peramivir is only used in severe cases who are unable to use oral or inhaled antivirals due to disturbed consciousness or other complications. So some of the patients who had been prescribed with peramivir in these two influenza seasons could have used Tamiflu before and started using peramivir due to progression in symptoms or deterioration in consciousness. The death of patients could be associated with disease severity, though more studies are needed to prove the assumption.

As mentioned above, peramivir is an intravenous injecting antivirals which can be used in patients unable to use oral or inhaled drugs [8]. The efficacy in outpatients with influenza infection was not inferior to Tamiflu [9]. Doubled dose is recommended in complicated infection. In our study, 24 patients were prescribed with doubled dose (600 mg) and 11 of them died. Doubled dose (600mg per day) was found to shorten the disease course than standard dose (300 mg per day) in one study [10]. More studies are necessary to evaluate the association between dose and prognosis.

Conclusion

In elderly, young children, patients with cardiopulmonary, kidney, metabolic diseases, and anemia, or immune compromised hosts, complicated influenza infection and associated death are more common. Because these patients may need mechanical ventilator and extra corporeal membrane oxygenator (ECMO) to treat complications such as pneumonia or acute respiratory distress syndrome, they may have difficulties in using oral or inhaled antivirals or have an expected lower drug absorption rate and attending physicians should consider use of peramivir and explain to the patient or his family the pros and cons and application process as a treatment alternative.

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