Influenza in Taiwan: seasonality and vaccine strain match

Yu-Chia Hsieh[1], Hour-Young Chen[2], Jer-Jea Yen[3], Ding-Ping Liu[3], Luan-Yin Chang[4], Chun-Yi Lu[4], Pei-Lan Shao[4], Chin-Yun Lee[4], Li-Min Huang[4]

[1]Section of Infection, Department of Medicine, Wan-Fang Hospital, Taipei Medical University, Taipei;
[2]Center for Research and Diagnostics, and [3]Immunization Division, Center of Disease Control, Taipei; and
[4]Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

This article explores seasonality, epidemiology and dominant epidemic strains of influenza in Taiwan. Surveillance in Taiwan demonstrates that influenza is a disease which occurs throughout the year but has peak activity in winter. Due to the high mutability of influenza virus, effective vaccination is the best strategy for protection. Although the World Health Organization-recommended vaccine compositions usually matched with around 77% of circulating strains worldwide, the rate of matching in Taiwan has been markedly lower than this. Between 1997 and 2004 in Taiwan, the match rates were 82% for H1N1, 53% for H3N2, and 47% for influenza B virus. Furthermore, some world epidemic strains appeared earlier in Taiwan than in other countries. In view of Taiwan's proximity to southern China, which is thought to be the epicenter of influenza epidemics, vigilant surveillance and the development of regional strategies for the selection and manufacture of vaccine strains to improve influenza prevention are urgent requirements.

Key words: Disease outbreaks, epidemiology, influenza, influenza vaccines, review

Influenza viruses, probably existing for more than 2000 years, cause annual epidemics and the occasional pandemic of acute respiratory disease, leading to substantial morbidity, mortality and expense [1]. Influenza epidemics affect all age groups. The illness attack rate is about 10-20%, resulting in 50 million illnesses and up to 47,200 deaths in the United States each year and similar figures in Europe [2-6]. The rate of infection is highest in children, but most of the complications and deaths occur in persons aged more than 65 years and in patients with chronic disorders [7-9]. Influenza virus, first identified in 1933, comprises 3 types: A, B and C [10]. Type A and B are often associated with significant disease in humans. They have the capacity to undergo "antigenic drift", which is attributable to the accumulation of point mutations in 2 surface antigens, hemagglutinin and neuraminidase. The occurrence of mutations is facilitated by the lack of proofreading activity of viral RNA polymerase. Epidemics occur when the new variant strains enter a population in which few members possess antibody against the new antigen. Moreover, type A is also capable of inducing pandemics through a phenomenon known as "antigenic shift", which results from the reassortment of gene segments between human, avian or swine influenza viruses. A newly emerging influenza A virus subtype can pose a global threat to human health due to its potential to cause enormous morbidity and mortality. Accumulated evidence shows that influenza pandemics have occurred at unpredictable intervals over several centuries. In the last century, 3 influenza pandemics occurred. The Spanish Flu in 1918-1919, the most devastating of these events, was estimated to cause as many as 50 million deaths worldwide [11]. Another 2 pandemics, both originating from China, Asian flu in 1957-1958 and Hong Kong flu in 1968-1969 were caused by H2N2 and H3N2, respectively. These 2 more recent pandemic strains were shown to derive from gene reassortment between avian and human influenza virus [12]. In 1977, influenza A H1N1 re-emerged in Tianjin in China. It then spread to other parts of Asia, Europe, North America and the Southern hemisphere, but only attacked individuals aged less than 20 years. Since then, H1N1 and H3N2 have been co-circulating worldwide.

Influenza Seasonality and Epidemiology in Taiwan

Influenza usually causes winter epidemics in areas with temperate and cold climates. The influenza season lasts from December to March in the northern hemisphere,

Corresponding author: Dr. Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan.
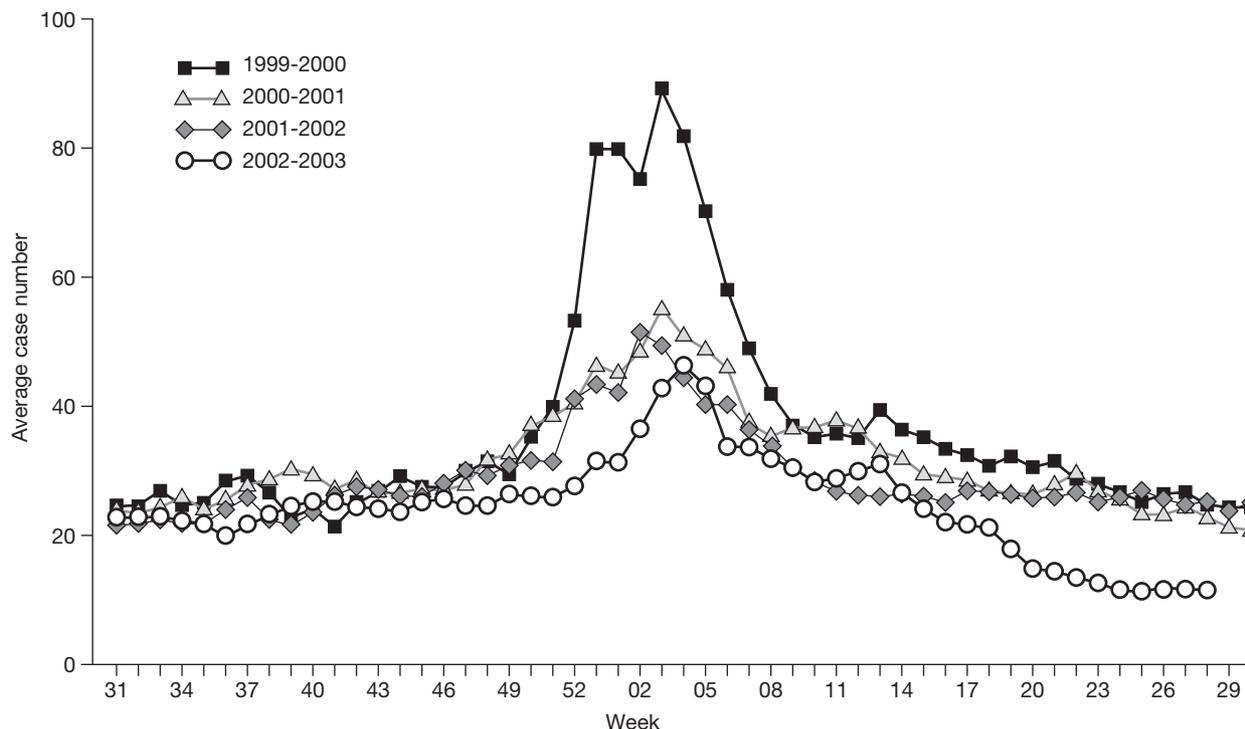*E-mail: lmhuang@ha.mc.ntu.edu.tw*

Fig. 1. Weekly average case numbers of influenza-like illness reported by each sentinel physician in Taiwan during 1999-2003.

and from June to September in the southern hemisphere. In tropical and subtropical areas, influenza epidemics can occur either throughout the year with no distinct seasonality or visible excess mortality, or twice a year, with the more intense activity during the rainy season.

Influenza is a seasonal disease in Taiwan. Most cases occur in winter, usually from December to March. The influenza activity usually starts in northern Taiwan in November, then spreads to central and southern Taiwan. According to the sentinel physician surveillance system established by the Center for Disease Control in Taiwan, influenza-like illness has a first peak around Chinese New Year which usually falls in early February, the second wave peaks in March, and then a decline occurs before the coming of summer. During 1999-2003, the weekly case numbers of influenza-like illness reported by each sentinel physician surveillance system ranged from 43.17 to 88.46 (Fig. 1). Children younger than 4 years had the most reported cases among all ages, followed by persons aged between 5 and 24 years and those older than 65 years (Fig. 2). From 1980 to 2001, there were 2000 to 3817 excess deaths each year related to pneumonia and influenza in people older than 65 years. On average, the culture yield rate of influenza virus among the samples sent for respiratory pathogen isolation was 6%, but this rate could be as high as 45%

in the epidemic season. Although influenza mainly occurs in the winter in Taiwan, sporadic cases occur throughout the year.

Among all the influenza virus isolates, influenza virus type A was more frequently seen than influenza virus type B. Several epidemic strains re-emerged after disappearance for several years. Among the epidemic strains in Taiwan, A/H3N2 had the highest antigenic variation, followed by type B and A/H1N1 [13].

Influenza Vaccine

Inactivated influenza vaccine has been used as a measure to control influenza outbreaks since the 1930s [14]. Many studies have investigated the effectiveness of influenza vaccine. Generally, the illness is less severe in vaccinated people. A randomized, placebo-controlled study of healthy adult workers in the United States showed that vaccination reduced upper respiratory illness by 25%, illness-related work absenteeism by 43%, and physician visits by 44% with a resulting cost savings of $46.85 per person vaccinated [15]. Vaccination in persons aged 65 years or older was estimated to reduce rates of hospitalization for pneumonia and influenza by 18-52% and death from all causes by 27-70% [16-20].
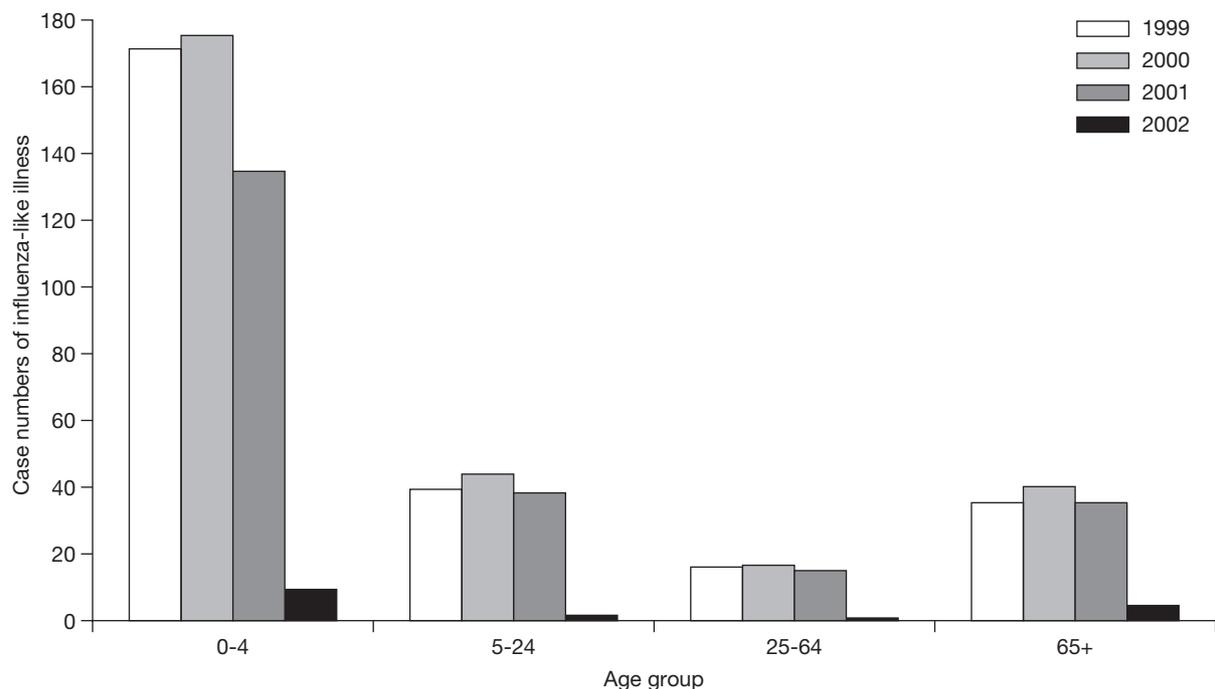
Fig. 2. Case numbers of influenza-like illness in Taiwan stratified by age group during 1999-2002.

Vaccination or re-infection in immunologically primed individuals with antigen-related strains will induce cross-reactive antibody (original antigenic sin). In the elderly, however, antibody elicited by vaccination is usually less robust than in healthy adults due to immunosenescence. Despite its limited efficacy, vaccination is still a cost-saving intervention for preventing influenza disease in older people.

Inactivated influenza vaccine has some pitfalls, including the necessity of predicting the coming epidemic strains every year, short duration of protection, and the costs associated with administering yearly vaccination. The recent focus on influenza vaccine has been on the use of cold-adapted intranasal live, attenuated vaccine (CAIV). CAIV, resembling the natural infection with wild-type influenza virus, can induce broader immunity against antigenically drifted influenza strains and a longer duration of immunity [21,22].

Strain Matching

The effectiveness and efficacy of influenza vaccine depends greatly upon whether vaccine antigens match the prevalent circulating influenza virus strains. The vaccine can achieve effectiveness rates of 70-90% for a homologous strain in healthy persons. If there is a considerable mismatch between vaccine antigen and a circulating strain, the protective efficacy of the vaccine will be unsatisfactory. This phenomenon is particularly obvious in the elderly as cross-reactive antibody induced by vaccine declines with increasing age [23]. Hence, update of the vaccine strains to cope with the ever-changing influenza virus spectrum in circulation is mandatory. In 1947, a new influenza A (A/FM/1/46 H1N1) spread throughout the world and the vaccines in use at that time were ineffective. In April 1947, the World Health Organization (WHO) established a worldwide network, the World Influenza Center (WIC), which has been used to inform governments about the correct choice of vaccine strains since 1953. The principle of choosing vaccine strains is based on antigenic and genetic data of virus strains isolated worldwide compared with data from strains isolated in previous years. The antigenic analysis is characterized by reactivity in hemagglutination inhibition assay with ferret antisera, the results of which are in good agreement with those derived using sera from human vaccines [23]. When epidemiologic data indicate that a new variant has the potential to spread and cause disease, the ability of the current vaccine to induce adequate antibody response in humans to the newly detected viruses must be evaluated. Usually, the choice of components of influenza virus vaccine for the coming influenza season in the northern hemisphere is made in February in order

Table 1. Degree of matching between World Health Organization (WHO)-recommended influenza A vaccine strains and circulating strains

H1N1 vaccine and epidemic strains (matching rate 82%, 14/17)				H3N2 vaccine and epidemic strains (matching rate 53%, 9/17)			
Years	WHO recommended	World strain	Taiwan isolates	Years	WHO recommended	World strain	Taiwan isolates
1987/88	Singapore/6/86	Singapore/6/86	Singapore/6/86	1987/88	Leningrad/360/86	Sichuan/2/87[a]	NA
1988/89	Singapore/6/86	Singapore/6/86	NA	1988/89	Sichuan/2/87	Sichuan/2/87 + Shanghai/11/87	A/England/ 427/88[a]
1989/90	Singapore/6/86	Singapore/6/86	NA	1989/90	Shanghai/11/87	Shanghai/11/87	A/Shanghai/6/90
1990/91	Singapore/6/86	Singapore/6/86	A/Taiwan/1/86	1990/91	Guizhou/54/89	Beijing/353/89[a]	A/Texas/36/91[a]
1991/92	Singapore/6/86	Singapore/6/86	NA	1991/92	Beijing/353/89	Beijing/353/89	Beijing/353/89
1992/93	Singapore/6/86	Singapore/6/86	NA	1992/93	Beijing/353/89	Beijing/32/92[a]	Beijing/32/92[a]
1993/94	Singapore/6/86	Singapore/6/86	NA	1993/94	Beijing/32/92	Shangdong/9/93[a]	Beijing/353/89[a] + Beijing/32/92
1994/95	Singapore/6/86	Singapore/6/86	A/Taiwan/1/86	1994/95	Shangdong/9/93	Johannesburg/ 33/94[a]	NA
1995/96	Singapore/6/86	Singapore/6/86	A/Taiwan/1/86	1995/96	Johannesburg/ 33/94	Johannesburg/ 33/94	Shangdong/9/93[a] + Johannesburg/ 33/94
1996/97	Singapore/6/86	Singapore/6/86	Beijing/262/95[a,b] + A/Taiwan/1/86	1996/97	Wuhan/359/95	Wuhan/359/95	Wuhan/359/95
1997/98	Bayern/7/95	Beijing/262/95[a] + Bayern/7/95	Beijing/262/95[a]	1997/98	Wuhan/359/95	Sydney/05/97[a]	Sydney/05/97[a]
1998/99	Beijing/262/95	Beijing/262/95	Beijing/262/95	1998/99	Sydney/05/97	Sydney/05/97	Sydney/05/97
1999/00	Beijing/262/95	New Caledonia/ 20/99[a]	New Caledonia/ 20/99427/88[a] + Beijing/262/95[a]	1999/00	Sydney/05/97	Sydney/05/97	Sydney/05/97 + Moscow/10/99[a,b]
2000/01	New Caledonia/ 20/99	New Caledonia/ 20/99	New Caledonia/ 20/99	2000/01	Moscow/10/99	Moscow/10/99	Moscow/10/99
2001/02	New Caledonia/ 20/99	New Caledonia/ 20/99	New Caledonia/ 20/99	2001/02	Moscow/10/99	Moscow/10/99	Moscow/10/99
2002/03	New Caledonia/ 20/99	New Caledonia/ 20/99	New Caledonia/ 20/99	2002/03	Moscow/10/99	Moscow/10/99	Moscow/10/99
2003/04	New Caledonia/ 20/99	New Caledonia/ 20/99	New Caledonia/ 20/99	2003/04	Moscow/10/99	Moscow/10/99 + Fujian/411/2002[a]	Fujian/411/ 2002[a]

Abbreviation: NA = no available data
[a]Mismatch between WHO-recommended strains and world strains or epidemic strains in Taiwan.
[b]Strains which circulated in Taiwan earlier than in other countries of the world.

to leave enough time for production, testing, and distribution. If an antigenic mismatch is observed, the WHO will recommend the inclusion of the newly emerged virus strain in the influenza vaccine. In the past, there was a high degree of matching between WHO-recommended vaccine strains and epidemic strains in most seasons. The match rate from 1987-1996 was around 77% worldwide [24]. For example, from 1980-1993 in Canada, the average match rate between laboratory-confirmed influenza isolates and vaccine antigen was 71.2% (98.6% in influenza virus type A H1N1, 64.9% in influenza virus type A H3N2, and 64.9% in influenza virus type B) [24].

Strain Match in Taiwan

Surveillance data demonstrated a higher mismatch rate between the WHO-recommended vaccine strains for the northern hemisphere and predominantly circulating viruses in Taiwan than in western countries. For example, analysis of the WHO-recommended vaccine strains and predominant virus in Taiwan from 1987/1988 to 2003/2004 revealed the matching rates in Taiwan were inferior to those observed in Canada, with H1N1 matching rates for 14 of the 17 years of 82% for Taiwan vs 98.6% for Canada, H3N3 matching rates in 9 of the 17 years of 53% vs 64.9%, and virus type B matching

Table 2. Degree of matching between World Health Organization (WHO)-recommended influenza B vaccine strains and circulating strains

Years	Influenza B vaccine and epidemic strains (matching rate 47%, 8/17)		
	WHO recommended	World strain	Taiwan isolates
1987/88	Ann Arbor/1/86	Beijing/1/87[a]	USSR/2/87[a] + Victoria/2/87[a]
1988/89	Beijing/1/87	Beijing/1/87	Yamagata/16/88[a,b]
1989/90	Yamagata/16/88	Yamagata/16/88	Yamagata/16/88 + Panama/45/90[a,b]
1990/91	Yamagata/16/88	Yamagata/16/88	Qingdao/102/91
1991/92	Yamagata/16/88 or Panama/45/90	Yamagata/16/88 or Panama/45/90	Panama/45/90
1992/93	Yamagata/16/88 or Panama/45/90	Yamagata/16/88	Panama/45/90
1993/94	Panama/45/90	Panama/45/90	Panama/45/90
1994/95	Panama/45/90	Beijing/184/93[a]	Beijing/184/93[a]
1995/96	Beijing/184/93	Beijing/184/93	Beijing/184/93
1996/97	Beijing/184/93	Beijing/184/93	Beijing/184/93 + Guangdong/8/93[a]
1997/98	Beijing/184/93	Harbin/184/93	Shangdong/07/97[a] + Victoria/02/87[a]
1998/99	Beijing/184/93	Beijing/184/93	Beijing/184/93 + Harbin/184/94
1999/00	Shangdong/07/97 or Beijing/184/93	Beijing/184/93	Beijing/184/93 + Shangdong/07/97
2000/01	Beijing/184/93	Beijing/184/93	Beijing/184/93 + Sichuan/379/99[a,b]
2001/02	Sichuan/379/99	Sichuan/379/99	Hong Kong/330/2001[a,b]
2002/03	Hong Kong/330/2001	Hong Kong/330/2001	Hong Kong/330/2001
2003/04	Hong Kong/330/2001	Hong Kong/330/2001	B/Sichuan/379/99

[a]Mismatch between WHO-recommended strains and world strains or epidemic strains in Taiwan.
[b]Indicates strains which circulated in Taiwan earlier than in other countries in the world.

rates in 8 of the 17 years of 47% vs 64.9% (Table 1 and Table 2). Some world epidemic strains also appeared in Taiwan earlier than in other countries. For example, in 1997-1998, the WHO-recommended A/Bayern/7/95 (H1N1) to be a vaccine strain. In the following years, France, Senegal, South Africa, and the United States first reported isolation of A/Beijing/262/95-like virus, which had appeared in Taiwan in 1996-1997. Hence, A/Beijing/262/95 became a vaccine strain in 1998-1999 because it could induce adequate antibodies against both A/Beijing/262/95 and A/Bayern/7/95 strains, while vaccination with A/Bayern/7/95 could not induce adequate antibodies against both strains. Other strains found worldwide, such as A/Moscow/10/99 (H3N2) in 2000-2001, B/Yamagata/16/88 in 1989-1990, B/Sichuan/379/99 in 2001-2002 and B/Hong Kong/330/2001 in 2002-2003 have also been detected earlier in Taiwan than in other countries. This phenomenon of earlier appearance of epidemic strains in Taiwan than other parts of world stems from the fact that Taiwan is closer to the world influenza epicenter, China, where significant influenza antigenic drift variants emerge [25, 26]. Due to the lower strain match rate, the vaccine strain composition suggested by the WHO is likely to be less appropriate for people in Taiwan and nearby regions. Asia, especially Taiwan and nearby countries such as Japan and Hong Kong, need to have programs in place

to predict their own influenza vaccine strains. The importance of ongoing active influenza surveillance in Taiwan should be emphasized in order to best control future influenza outbreaks and provide sentinel data as quickly as possible to other countries.

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