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Centennial review of influenza in Taiwan

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ABSTRACT

The history of influenza in Taiwan can be traced up to the 1918 H1N1 Spanish flu pandemic, followed by several others including the 1957 H2N2, 1968 H3N2, and the 2009 new H1N1. A couple of avian influenza viruses of H5N1 and H7N9 also posed threats to the general public in Taiwan in the two recent decades. Nevertheless, two seasonal influenza A viruses and two lineages of influenza B viruses continue causing annual endemics one after the other, or appearing simultaneously. Their interplay provided interesting evolutionary trajectories for these viruses, allowing us to computationally model their global migrations together with the data collected elsewhere from different geographical locations. An island-wide laboratory-based surveillance network was also established since 2000 for systematically collecting and managing the disease and molecular epidemiology. Experiences learned from this network helped in encountering and managing newly emerging infectious diseases, including the 2003 SARS and 2009 H1N1 outbreaks.

Brief history of global influenza virus outbreaks

There are four types of influenza viruses: types A, B, C, and D. Influenza A, B and C viruses infect humans. Of these types, only type A viruses have caused pandemics, resulting in considerable impact on human health globally. Influenza B causes seasonal epidemics while influenza C causes mild human infections with minimal public health impact. The

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most well-known pandemic in human history was the 1918 H1N1 pandemic, when an H1N1 virus that was believed to have originated from birds adapted to humans resulting in more than 50 million deaths worldwide. In 1957, another pandemic known as the "Asian flu" caused by an H2N2 influenza A virus resulted in another million deaths. In 1968 the aforementioned H2N2 virus acquired a novel haemagglutinin and PB2 gene segment from avian influenza virus origin to cause another pandemic that was first detected in Hong Kong and then spread to other regions in Asia and globally. In 1977, an H1N1 virus almost identical to seasonal H1N1 viruses circulating in the 1950s re-emerged and led to epidemics worldwide. Since that time, the two influenza A viruses, H1N1 and H3N2, have circulated worldwide as the major human influenza A seasonal flu viruses resulting in annual epidemics or endemics. In 2009, a new strain of H1N1 emerged and caused the most recent pandemic in human history. This new H1N1 virus was initially called a "swine-origin" influenza virus because its gene segments are derived from swine influenza viruses. The 2009 pandemic virus replaced the previous seasonal H1N1 viruses that was active for three decades prior to 2008 and since then has co-circulated in humans with influenza A H3N2 and influenza B viruses.

Pandemics and epidemics in Taiwan

1918 H1N1 pandemic

Although Taiwan, which comprises several islands located in the western Pacific Ocean, is relatively isolated from other countries, influenza pandemics have still affected its inhabitants. During the 1918 H1N1 influenza pandemic, Taiwan was governed by Japan. Previous studies have noted that this pandemic may have caused more than 25,000 deaths in Taiwan [1,2]. Similar to the transmission route of the 1918 influenza virus in the United States, this H1N1 virus may have initially spread in military bases or through migration of troops. According to the reports of a Japanese medical officer Arai Megumi in 1918–19 [Fig. 1], the earliest cases of the influenza infection may have originated in Keelung Harbor in northern Taiwan in June 1918 before spreading to other parts in Taiwan [2]. Notably, the number of cases decreased in 1919 but then considerably increased from December 1919 to February 1920, resulting in more than 19,000 deaths. During the pandemic, schools in Taiwan were closed for several days because of the high infection rate and prevalence of severe respiratory symptoms among students and faculty members. In contrast to Western countries, the mortality rate for young children (aged less than 5 years) was higher than that for young adults (aged 20–30 years) [2]. Insufficient public hygiene and low health care standards during this period may have contributed to the high mortality rate of the pandemic; further research is required to elucidate the statistics regarding disease severity and mortality related to the pandemic. The high mortality rate among infected individuals may have been a result of the low-quality health care system, including a lack of physicians and an excessive burden on the health care system [3]. Hsieh (2009) estimated that the percentage of excess deaths was 1.38% over the entire population during 1918–20 in Taiwan and concluded that the 1918 influenza pandemic caused significant mortality in Taiwan [4]. Wilson Smith (1933) isolated the causative agent of human influenza in 1933.

1957 H2N2 pandemic

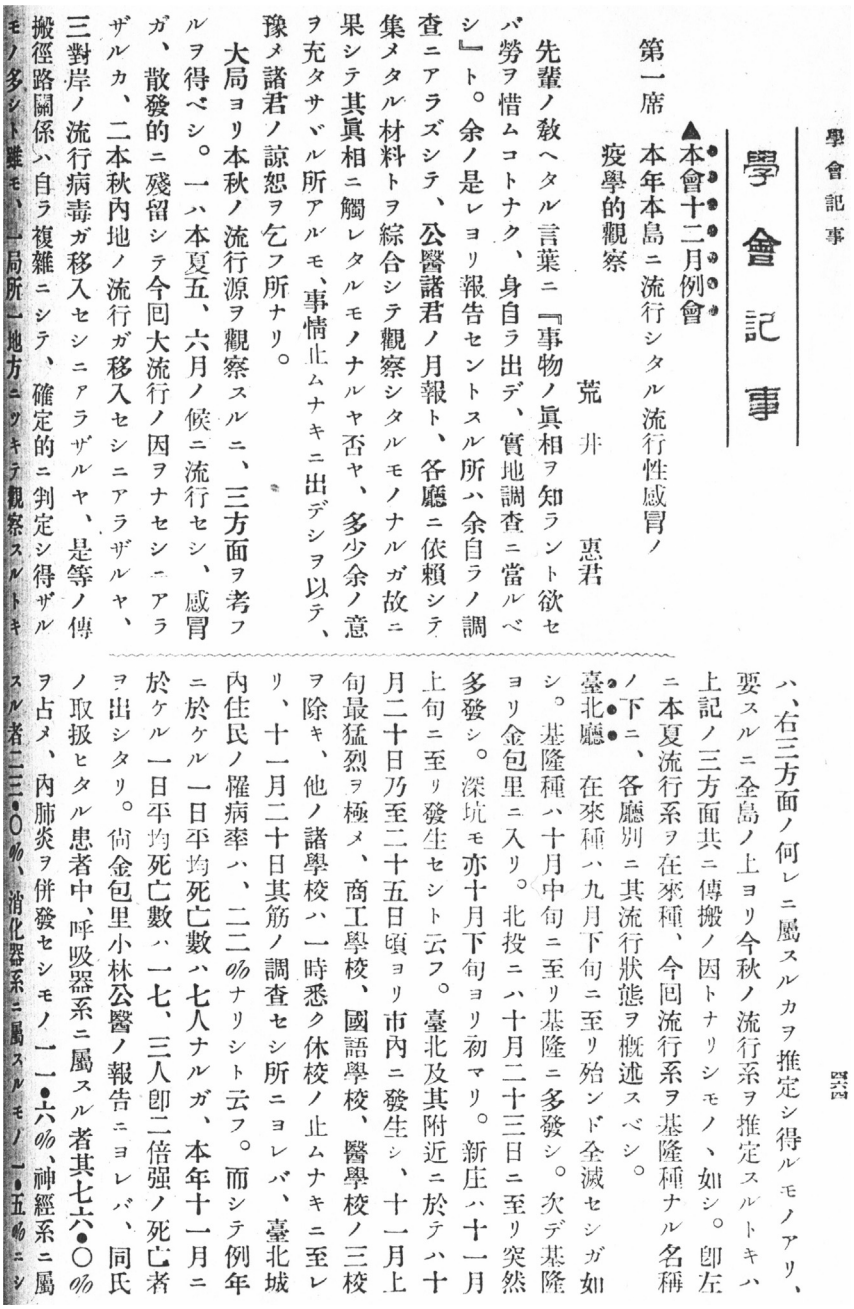
The virus that caused the 1957 Asian flu pandemic was recognized as an influenza A virus [5] of different A subtype designated as H2N2. The 1957 pandemic, called the "Asian flu" originated in southeast China and then spread to other Asian countries such as Singapore and Hong Kong and then worldwide [6]. Later studies revealed that the H2N2 pandemic virus originated by the previously circulating human H1N1 acquiring novel haemagglutinin (HA), neuraminidase (NA) and PB1 gene segments from an avian influenza virus [7]. Several strains of the influenza A virus related to the pandemic were isolated in Taiwan during the pandemic [8,9]. In addition, there was evidence that an antigenic drift might have occurred in the later isolates of H2N2 viruses in Taiwan [1,10]. Although H2N2 viruses have not circulated among humans since 1968, several studies have warned of the risks of the re-emergence of an H2N2 virus as a novel pandemic [11,12].

1968 H3N2 pandemic

In 1968, a new worldwide pandemic was caused by an H3N2 influenza A virus. Because the virus was first isolated in Hong Kong, the pandemic caused by this virus has been called the "Hong Kong influenza" pandemic. Previous studies have demonstrated that the H3N2 virus was derived by genetic reassortment with the previously circulating human H2N2 virus acquiring HA and PB1 gene segments from an avian influenza A virus [13,14]. During 1968–71, the number of deaths related to influenza infection in Taiwan increased, which may indicate the burden of pandemics on the islands [1]. Contemporaneous with the emergence of the H3N2 pandemic in Taiwan, the virus was also isolated in pigs, the first indication of reverse zoonosis, with pigs acquiring human influenza viruses [15]. Several influenza A viruses closely related to human A/Hong Kong/68 (H3N2) were also isolated in dogs in Taiwan in 1971 [16]. Since 1968, the pandemic H3N2 virus has continuously circulated among humans as a seasonal influenza virus. Antigenic drift of this H3N2 has occurred.

Reappearance of H1N1 in 1977

Although the 1968 pandemic strain of H3N2 adapted to humans and became a seasonal influenza virus, an H1N1 virus reappeared and caused epidemics in 1977. Because the first report of the outbreak was from the Union of Soviet Socialist Republics [17], the pandemic caused by the H1N1 virus has been called the "Russian flu". Genetic and antigenic analyses have revealed that this H1N1 virus was closely related in all eight gene segments to the H1N1 viruses isolated in humans during the 1950–51 Scandinavian epidemics [18,19]. Therefore, this virus is considered to have re-emerged from human



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第一席　本年本島ニ流行シタル流行性感冒ノ疫學的觀察　荒井恵君

先輩ノ敎ヘタル言葉ニ『事物ノ眞相ヲ知ラント欲セバ勞ヲ惜ムコトナク、身自ラ出デ、實地調査ニ當ルベシ』ト。余ノ是レヨリ報告セントスル所ハ余自ラノ調査ニアラズシテ、公醫諸君ノ月報ト、各廳ニ依賴シテ集メタル材料トヲ綜合シテ觀察シタルモノナルガ故ニ果シテ其眞相ニ觸レタルモノナルヤ否ヤ、多少余ノ意ヲ充タサヾル所アルモ、事情止ムナキニ出デシヨリ以テ、豫メ諸君ノ諒恕ヲ乞フ所ナリ。

大局ヨリ本秋ノ流行源ヲ觀察スルニ、三方面ヲ考フルヲ得ベシ。一ハ本夏五、六月ノ候ニ流行セシ、感冒ガ、散發的ニ殘留シテ今回大流行ノ因ヲナセシニアラザルカ、二本秋内地ノ流行ガ移入セシニアラザルヤ、三對岸ノ流行病毒ガ移入セシニアラザルヤ、是等ノ傳搬徑路關係ハ自ラ複雜ニシテ、確定的ニ判定シ得ザルモノ多シト雖モ、一局所一地方ニツキテ觀察スルトキスル者二二・〇%、消化器系ニ屬スルモノ一・五%ニシテ、右三方面ノ何レニ屬スルカヲ推定シ得ルモノアリ、要スルニ全島ノ上ヨリ今秋ノ流行系ヲ推定スルトキハ上記ノ三方面共ニ傳搬ノ因トナリシモノヽ如シ。卽左ニ本夏流行系ヲ在來種、今回流行系ヲ基隆種ナル名稱ノ下ニ、各廳別ニ其流行狀態ヲ概述スベシ。

臺北廳　在來種ハ九月下旬ニ至リ殆ンド全滅セシガ如シ。基隆種ハ十月中旬ニ至リ基隆ニ多發シ。次デ基隆ヨリ金包里ニ入リ。北投ニハ十月二十三日ニ至リ突然多發シ。深坑モ亦十月下旬ヨリ初マリ。新庄ハ十一月上旬ニ至リ發生セシト云フ。臺北及其附近ニ於テハ十月二十日乃至二十五日頃ヨリ市内ニ發生シ、十一月上旬最猛烈ヲ極メ、商工學校、國語學校、醫學校ノ三校ヲ除キ、他ノ諸學校ハ一時悉ク休校ノ止ムナキニ至レリ、十一月二十日其筋ノ調査セシ所ニヨレバ、臺北城内住民ノ罹病率ハ、二二%ナリシト云フ。而シテ例年ニ於ケル一日平均死亡數ハ七人ナルガ、本年十一月ニ於ケル一日平均死亡數ハ一七、三人卽二倍强ノ死亡者ヲ出シタリ。尙金包里小林公醫ノ報告ニヨレバ、同氏ノ取扱ヒタル患者中、呼吸器系ニ屬スル者其七六・〇%ヲ占メ、内肺炎ヲ併發セシモノ一一・六%、神經系ニ屬

Fig. 1 **Part of the original manuscript (in Japanese) describing the 1918 influenza pandemic in Taiwan reported by a Japanese medical officer, Arai Megumi, published in the Journal of the Formosan Medical Association, 1919. (The image was provided by the Formosan Medical Association.)**

The author of the report discussed the possible origins of the infectious agent that caused the pandemic in Taiwan, including import from elsewhere. By the author's investigation, the outbreaks in Northern Taiwan were initiated in mid-October from Keelung (a harbor city northeast of Taipei) and the adjacent towns, then spread to Taipei city in late October. According to the report, the outbreak resulted in schools being closed in Taipei city in early November, and 22% of the population in the city possibly infected by the agent of influenza. In addition, compared to the average mortality in the city, the death count was increased more than 2- fold in November, from an average of 7 in previous years, to 17.3 per day in 1918.

seasonal H1N1 viruses that circulated in the 1950s. Several possibilities have been suggested for the origin and re-emergence of the H1N1 virus, including possibilities of a laboratory accident or the virus deriving from a vaccine trial attempting to generate H1N1 vaccines, possibly as a response to the 1976 swine flu incident in the USA [20]. Since its emergence in 1977, the H1N1 virus became a seasonal influenza virus that co-circulated with H3N2 viruses worldwide, including in Taiwan, until the novel 2009 H1N1 pandemic virus replaced this H1N1 virus.

2009 H1N1 pandemic

In 2009, two patients with human respiratory illness in Southern California were identified to be infected with a novel H1N1 influenza A virus that was genetically similar to the swine-origin H1N1 viruses [21]. This pandemic which started in Mexico rapidly spread to other countries. Sequencing and phylogenetic analysis demonstrated that the virus, later named A (H1N1)pdm09, was generated by genetic reassortment with gene segments being derived from North American avian, human H3N2, classic swine, and Eurasian swine influenza A viruses [22–24]. In Taiwan, the first case of human infection with A (H1N1)pdm09 was reported in May 2009 [25]. Because of the lack of prior immunity to this virus, especially in younger children, the novel virus spread rapidly in Taiwan [25] in the second half of 2009. Another A (H1N1)pdm09 outbreak occurred in the following winter season of 2010/2011, with less number of viruses being isolated. Interestingly, the severe influenza and pneumonia/influenza related death from this virus seemed to be more prominent in the first few weeks in 2011 rather than those in 2009 when it was firstly introduced into Taiwan (https://nidss.cdc.gov.tw/ch/Default.aspx?op=2). It is possible that the virological diagnostic effort was more vigorous in 2009 and more cases were diagnosed with clinical criteria in 2011. Because of the SARS outbreak that had occurred in Taiwan in 2003, Taiwan was adequately prepared for managing pandemics [26]. Interventions used in response to the pandemic included school closures [27]. In addition, vaccines and rapid diagnostic tests were made widely available in 2009 [28,29]. In 2011, the World Health Organization (WHO) announced the end of the H1N1 pandemic, the A (H1N1)pdm09 virus now being recognized as a seasonal influenza virus. At the time of writing this review, the 2009 pandemic H1N1 virus has replaced the previous seasonal H1N1 virus that circulated from 1977 up to 2009 in Taiwan [30].

Threats related to avian influenza viruses H5N1 and H7N9

In 1997, cases of human infection with a highly pathogenic avian influenza A virus (H5N1) were reported in Hong Kong [31]. Although this outbreak in humans was contained by the depopulation of all poultry in Hong Kong in December 1997, subsequent surveillance in Hong Kong on imported poultry revealed that the virus continued to circulate in the wider region. The virus spread to multiple Asian countries, and after 2005, was spread by wild bird migration to South Asia, the Middle East and Africa. Up to now the virus has caused thousands of poultry outbreaks and 860 zoonotic infections have been reported, resulting in 454 deaths (http://www.who.int/influenza/human_animal_interface/2018_01_25_tableH5N1.pdf?ua=1). Although no diagnoses of human H5N1 infection has been reported in Taiwan at the time of writing this review, this avian influenza virus is a constant threat to public health. Several imported cases of infection with another avian influenza A virus (H7N9) in humans have been reported in Taiwan since 2013 [32,33]. Infection with the avian H7N9 virus in humans with severe respiratory complications was first reported in China in 2013 [34,35]. According to information updated in February 2018 from the Food and Agriculture Organization of the United Nations, 1625 human cases of H7N9 infection have been confirmed, including 621 fatalities (http://www.fao.org/ag/againfo/programmes/en/empres/h7n9/situation_update.html). Because the avian H7N9 virus causes severe disease in humans, the Taiwanese government has undertaken considerable efforts to prevent the virus from being imported and spread throughout the islands. Additionally, the government has established surveillance systems and early diagnostic technology to monitor the avian influenza viruses throughout Taiwan.

Epidemics of seasonal influenza viruses in Taiwan

Seasonal influenza A and B viruses circulate worldwide, infecting 5–10% of adults and 20–30% of children annually [36], and these viruses are responsible for up to half a million deaths every year. In Taiwan, an island-wide laboratory-based surveillance network of 11 clinical virology laboratories was established in 2000 under coordination of the Taiwan Centers for Disease Control (CDC) and this network has substantially contributed to the control of influenza virus infections [37].

Influenza epidemic waves from 2000 to 2015

At the time of writing this review, the major lineages of influenza viruses responsible for influenza epidemics in Taiwan are the H3N2 and H1N1 subtypes of influenza A viruses and the Victoria and Yamagata lineages of influenza B viruses. The peak circulation of these viruses is usually detected during the winter months (December to February), although summer outbreaks occasionally occur [37]. We summarized the circulating viruses and summer epidemics from 2000–01 to 2017–18 in Table 1. The dominant lineages in the 2000–01 and 2001–02 seasons were the influenza B and H1N1 viruses, respectively, those in 2002–03 and 2003–04 were H3N2 [37], and in 2004–05 H3N2 co-circulated with influenza B viruses [38,39]. In the subsequent period from 2005–06 to 2008–09, the H1N1 subtype prevailed (except for the co-circulation of H3N2 and influenza B viruses in 2006–07) [38,39]. The 2009 pandemic was caused by the novel A (H1N1) pdm09 virus, which was generated by reassortment of several influenza viruses. This new H1N1 virus continued to be the dominant influenza virus in the two subsequent winters [40] and replaced the previous seasonal H1N1 virus to become the new seasonal H1N1 virus. Although influenza B viruses circulated in 2011–12, a summer epidemic of H3N2 occurred in 2012 [41]. Subsequently, H3N2 dominated the following three flu seasons in 2012–13, 2013–14, and 2014–15. Notably, three summer H3N2 epidemics in 2005, 2007, and 2012 followed the circulation of influenza B viruses during the winters of 2004–05, 2006–07, and 2011–12, respectively. Thus, new antigenic variants that generate in summer might be the progenitors of epidemic strains the following winter [39].

Summer outbreaks and prediction of their global migrations

In addition to Taiwan, summer influenza outbreaks have been reported in Okinawa (Japan), Hong Kong, Mexico, Pakistan, and Vietnam [42]. The circulating subtypes in Okinawa are

Table 1 Circulating viruses and summer epidemics from 2000 – 01 to 2017–18 in Taiwan.

Circulating viruses	2000 –01	2001 –02	2002 –03	2003 –04	2004 –05	2005 –06	2006 –07	2007 –08	2008 –09	2009 –10	2010 –11	2011 –12	2012 –13	2013 –14	2014 –15	2015 –16	2016 –17	2017 –18
Influenza A H1N1		✓				✓		✓	✓	✓	✓					✓		
Influenza A H3N2			✓	✓	◯		◯			◯		◯	✓	✓	✓		✓◯	
Influenza B	✓	◯			✓		✓					✓						✓

✓ Dominant virus
◯ Summer epidemic (e.g., an epidemic wave of influenza B viruses in summer 2002 following the 2001–02 flu season)

similar to those in Taiwan and Hong Kong; however, the sources and migrations of summer epidemics remain unknown [42]. With the rapid development of sequencing technologies, phylodynamic and phylogeographic methods have become widely used frameworks for analyzing viral evolution and epidemiology from large-scale sequences; these methods combine multidisciplinary perspectives such as population genetics, evolutionary and epidemiological modeling, and phylogenetic theory [43]. Such phylodynamic models have been applied to investigate the interactions between epidemiological and evolutionary processes [44,45] and the global migration patterns of H3N2 [46,47] and to identify how the H1N1 pandemic spread globally in 2009 [48]. A phylogeographic analysis based on sequences in a publicly available database was performed to simulate the spatiotemporal migrations of summer epidemics in Taiwan [49]. The results indicated that the 2005 summer epidemic originated in Korea and spread first to Hong Kong and subsequently to Taiwan. Additionally, the researchers suggested that the 2007 summer epidemic had originated in the western United States before migrating to the eastern United States and subsequently spreading to multiple Asian countries, including Taiwan. Although predictions generated using these methods may have been compromised by the availability of published sequence data in some time spans or countries [39,50], advancements in deep-sequencing technologies and computational analytics may improve understanding of the global spread of influenza viruses.

2015–16 H1N1 epidemic

In Taiwan, a most recent and serious seasonal H1N1 epidemic occurred in 2015–16, causing 163 deaths and 1663 severe infections (including influenza infection cases with pulmonary complications, neurologic complications, myocarditis, invasive bacterial infections, or pericarditis that required intensive care or resulting in death) from July 2015 to March 2016 [51]. It not only caused significant morbidity and mortality, but also resulted in 65 deaths and 676 severe cases in the age group of 50–64, those of robust immunity. Similar H1N1 outbreaks were also reported in other regions; for example, more than 39,000 infections and 2500 deaths occurred in 2015 in India [52], and in all federal districts of Russia, the rate of morbidity due to influenza and acute respiratory infection rapidly increased in the 2015–16 flu season and was higher than the epidemic threshold by 20% [53]. The longstanding A/California/7/2009 H1N1 vaccine strain utilized since 2009 was replaced by a newly recommended vaccine strain (A/Michigan/45/2015) in the following 2017 southern and 2017–18 northern hemisphere influenza seasons [54,55]. This suggests that selection of strains for vaccines against seasonal influenza viruses must be improved. Establishing a real-time monitoring system of genetic changes (e.g., Nextflu [56]) combined with rapid antigenic analysis can enable more effective selection of vaccine strains.

Circulating H3N2 and influenza B viruses from 2016 to 2018

The H3N2 virus circulated in the 2016–17 flu season in Taiwan and caused a summer epidemic in the late stage of the season [57,58] [Table 1]. Research has further indicated that an antigenic change was not the primary determinant of this H3N2 summer epidemic; rather, changes in fitness levels, reduced immunity, and climatic changes were possible contributors [58]. After this summer epidemic, influenza B viruses were the dominant viruses in the 2017–18 flu season, causing 610 severe infections and 88 deaths from October 2017 to March 2018 [59]. Notably, an unusually early influenza epidemic caused by the H3N2 virus co-circulating with the Yamagata lineage of influenza B viruses occurred during this period in Canada [60]. According to an Australian study [61], the H3N2 outbreak in 2017 was due to low vaccine efficacy. At the time of writing this review, this epidemic still prevailed, and thus further research is necessary to improve influenza vaccines. In conclusion, although the timing of influenza epidemics and the evolutionary pattern of influenza viruses remain unpredictable, recent computational techniques and sequencing platforms have provided a real-time and highly effective method for analyzing the rapid evolution of influenza viruses. Improving our understanding of and capacity to predict the evolution of influenza viruses could lead to the development of superior techniques for public health surveillance and effective recommendations for influenza vaccine strains in future seasons.

Discussion and future perspectives

As described in Section 3, the establishment of an island-wide laboratory-based surveillance network has facilitated

influenza epidemiology monitoring in Taiwan since 2000. The seamless collaboration between clinical virology laboratories at the medical centers that constitute this network enables the control of diseases and their pathogens. These laboratories can promptly identify viruses from clinical specimens through molecular analysis and virus genome sequencing, thereby generating massive genomic data-sets for molecular and evolutionary analytics. In addition, this network enables the management of newly emerging infectious diseases such as the 2003 SARS outbreak and 2009 H1N1 outbreak.

Although at the time of writing, no locally acquired H5N1 disease in humans had been reported in Taiwan, this avian influenza virus is a constant threat to public health. Several imported cases of human infection with an avian influenza A virus (H7N9) have been reported in Taiwan since 2013 [32,33] and zoonotic and potentially pandemic virus continues to cause concern. Because of these zoonotic threats, the Taiwanese government has undertaken considerable efforts to prevent these viruses from being imported and spread throughout poultry in the islands. For example, the government enforced a ban on slaughtering live poultry in traditional wet markets in June of 2013, although birds were already mostly butchered in the 79 licensed poultry slaughterhouses around the island. Additionally, the government has established surveillance systems and early diagnostic technology to monitor both human seasonal and avian influenza virus throughout Taiwan. In particular, advances in cell culture, reverse-transcriptase polymerase-chain-reaction (RT-PCR), sequencing technologies (such as the next-generation sequencing) and computational modeling should all contribute to help in our understanding of influenza epidemics.

Conflicts of interest

The authors declare no conflicts of interest.

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