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Understanding the complex seasonality of seasonal influenza A and B virus transmission: Evidence from six years of surveillance data in Shanghai, China

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ABSTRACT

Objectives: Understanding the complexity of influenza subtype seasonality is critical to promoting a suitable vaccination program. The aim of this study was to identify and compare the seasonality and epidemiological features of seasonal influenza subtypes after the 2009 A/H1N1 pandemic and to lay a foundation for further investigation into the social and environmental factors affecting seasonal influenza virus transmission.
Methods: Influenza-like illness (ILI) case surveillance was conducted in two sentinel hospitals in Pudong New Area, Shanghai between 2012 and 2018. Weekly data on ILI cases were analyzed. A time-series seasonal decomposition analysis was used to reveal the seasonality of influenza and epidemiological features among different subtypes.
Results: In total, 10 977 ILI patients were enrolled of whom 2385 (21.7%) had laboratory-confirmed influenza. Compared to influenza A (16.3%), influenza B (5.4%) was less frequently detected among the ILI patients ($p < 0.001$). Semiannual epidemic peaks were identified in four of the years during the 6-year study period, while only one annual epidemic peak was found in the other two years. An epidemic peak occurred in each winter season, and a secondary peak also occasionally occurred in summer or spring. A/H3N2 predominated in both summer and winter, while A/H1N1, B/Yamagata, and B/Victoria circulated almost exclusively in winter or spring. Two lineages of influenza B seemed to predominate in alternating years.
Conclusions: This study highlights the complexity of seasonal influenza virus activity in a subtropical region of China, presenting both semiannual and annual epidemic peaks in different years. The results of this study may provide further insight into possible improvements in the timing of influenza vaccination in Shanghai, China.

Introduction

Seasonal influenza causes a substantial mortality burden globally (Iuliano et al., 2018). Understanding the seasonality of influenza epidemics is critical to promoting a suitable vaccination program (Xu et al., 2017). In temperate regions, where influenza usually has a single epidemic peak in the winter, the seasonal pattern is clear and well documented (Finkelman et al., 2007; Viboud et al., 2004). In tropical and subtropical regions, the seasonal pattern is more complicated (Moura et al., 2009; Sanicas et al., 2014). Previous studies have revealed annual spring/summer or winter epidemics in some subtropical cities (Cheng et al., 2013; Hsieh et al., 2005) and semiannual epidemics in others (Iha et al., 2016; Liu et al., 2017a). Several studies have focused on exploring the changing patterns of influenza epidemics across climate zones or latitudes in different areas (Feng et al., 2012; Koul et al., 2014; Saha et al., 2016; Yu et al., 2013), comparing the characteristics of

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epidemics in neighboring cities to explore the potential influencing factors (Tang et al., 2018) and describing the epidemiological features of specific subtypes/lineages (Chan et al., 2013; Kuo et al., 2016; Yang et al., 2018a,b). However, few studies have discussed the complexity of influenza subtype seasonality in subtropical cities, especially after the A/H1N1 pandemic in 2009.

Currently, four antigenically distinct groups of influenza viruses, namely A/H3N2, A/H1N1, B/Victoria, and B/Yamagata, contribute to seasonal epidemics. Since 2009, the previously circulating seasonal H1N1 has been replaced by A/H1N1pdm09, which originated in swine. A/H3N2 has become predominant in most areas (Stohr, 2002). Several studies have demonstrated that genetic variants of A/H3N2 viruses are reseeded from East and Southeast Asia, and the antigenic characteristics of A/H3N2 viruses in other regions can be forecasted each year based on surveillance within East and Southeast Asia (Baumgartner et al., 2012; Russell et al., 2008). This finding highlights the importance of understanding influenza circulation patterns in East and Southeast Asia. In addition, the circulation patterns of the other three main influenza viruses differ substantially from those of A/H3N2, and their contributions to seasonal epidemics and dynamic patterns need to be further studied (Bedford et al., 2015). In particular, understanding the epidemiological characteristics of the two influenza B virus lineages would provide valuable insights into ways of modifying current influenza vaccination programs.

The aim of this study was to identify and compare the seasonality and epidemiological features of seasonal influenza subtypes after the 2009 A/H1N1 pandemic and to lay a foundation for further investigation into the social and environmental factors affecting seasonal influenza transmission, providing guidance to develop a more specific vaccination strategy.

Methods

The study was conducted in Pudong New Area, the largest district of Shanghai City, which is one of the largest and most developed international cities in the world. Shanghai is located in eastern China, and about one third of its population, around 5.5 million people, lived in Pudong New Area at the end of 2017 (Government P, 2017). This is a subtropical region at a latitude of 31.14°N and has four meteorologically distinct seasons every year (Figure 1). Spring starts in March and ends in May, with an average temperature of 14.5–16.2 °C. June, July, and August are the hot summer months (average temperature of 27.0–28.5 °C) with an annual rainy season lasting for about 2 weeks. Autumn extends from September to November, and the average temperature is about 19.3–20.8 °C. The remaining months (December, January, and February) constitute the cold winter, with an average temperature of 4.7–6.0 °C.

In order to control the potential risk of emerging or imported infectious disease outbreaks in Shanghai, all outpatients with a current or historical temperature over 38 °C are required to visit the fever clinics. From 2012 through 2018, trained clinicians in fever clinics at two hospitals in Pudong (Dongfang Hospital and Zhoupu Hospital) diagnosed all outpatients with an influenza-like illness (ILI) (patients attending within 10 days of symptom onset and presenting a fever ≥38 °C and cough or sore throat). The clinicians collected throat swab samples from the first three to five ILI patients every day. These two sentinel hospitals were the only ones conducting a national influenza surveillance project in Pudong New Area. Dongfang Hospital is a tertiary-level hospital conducting surveillance in children less than 14 years of age in the pediatric fever clinic, while Zhoupu Hospital is a secondary-level hospital conducting surveillance in patients of all age groups. The specimens were stored in 2 ml of viral transport medium (VTM, Yocon, Beijing, China) and transported at 2–8 °C within 24 h to Shanghai Pudong New Area Center for Disease Control and Prevention for laboratory testing. Nucleic acid was extracted and tested for influenza A/H1N1 (pdm09), A/H3N2, B/Yamagata, and B/Victoria using a reverse transcription PCR (RT-PCR) detection kit produced by Shanghai ZJ Bio-Tech Co., Ltd (Shanghai, China).

Information about each sampled patient, including sex, age, and date of illness onset, was collected by their physician and entered into the influenza surveillance information system established by the Chinese Centers for Disease Control and Prevention.

The weekly proportion of samples positive for influenza virus (influenza positivity rate) was the metric used in this study. This was defined as the ratio of the number of influenza-positive samples to the total number of samples tested each week. ISO week numbering was used in this study. This index was calculated in different surveillance years, seasons, age groups, and influenza

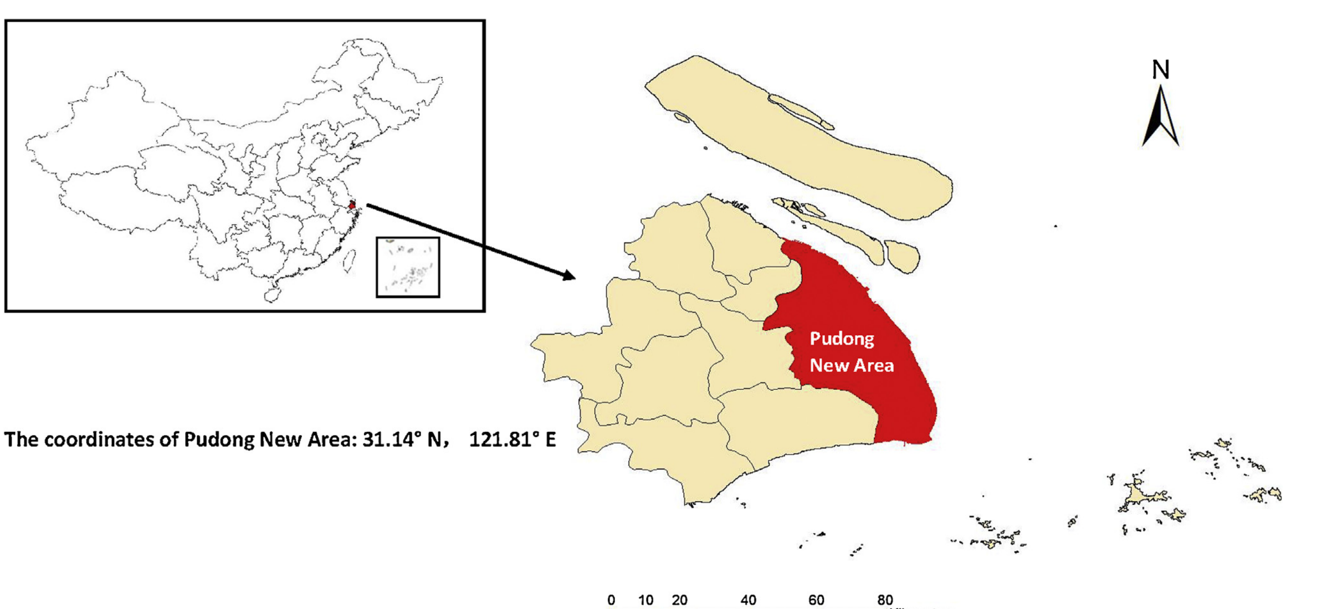

Figure 1. Location of Pudong New Area in Shanghai, China.

virus subtypes/lineages. For example, the influenza A/H3N2 positivity rate was calculated as follows:

$$\text{Influenza A/H3N2 positivity rate} = \frac{\text{number of samples positive for influenza A/H3N2}}{\text{total number of samples tested}} \times 100\%$$

A surveillance year was defined as the period ranging from week 23 of one year (approximately the week of June 1) to week 22 of the next year (approximately the week of May 31), based on influenza surveillance data.

In each surveillance year, the start of an influenza epidemic was defined as the first week during which the influenza positivity rate was higher than the annual average influenza positivity rate of that same year and remained above that level for at least four consecutive weeks. The end of an influenza epidemic was defined as the first week in an epidemic during which the influenza positivity rate was lower than the annual average influenza positivity rate of that same year and remained at that level for at least four consecutive weeks (Baumgartner et al., 2012). The predominant subtype/lineage was defined as the subtype/lineage with the highest positive proportion during each epidemic and remaining for at least four consecutive weeks. An epidemic could have a predominant single subtype/lineage or multiple ones.

Heat maps colored by influenza virus subtypes/lineages were created using the influenza positivity rate in each week of the year. A seasonal decomposition analysis was conducted to explore the seasonal pattern and periodicity of the influenza activity level stratified by subtype and lineage. Each time-series of the weekly influenza positivity rate values was decomposed into seasons, long-term trends, and irregular factors. The seasonality demonstrated the season during which the peak occurred, while the long-term trend showed the progression of the influenza series after the seasonal influence was excluded (Yang et al., 2018a,b). Decomposition procedures are able to describe the trend and seasonal factors in a time-series. In the present study, the systematic seasonal variations in influenza positivity rate were determined using this analysis, and the trend in influenza positivity rate during the overall study period was identified by removing any systematic seasonal variations (Hu et al., 2007; Zhang et al., 2017).

Data were analyzed using R 3.5.1 (R Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The Chi-square test or Fisher's exact test was used for categorical variables and the Wilcoxon rank sum test or Kruskal–Wallis test was used for continuous variables, as appropriate. p-Values of <0.05 were considered statistically significant.

Results

Descriptive analysis of ILI patients

From June 1, 2012 to May 31, 2018, 10 977 ILI patients were enrolled in this study. Their median age was 16 years (interquartile range = 7–32 years), and 5526 (50.3%) were male. The proportion of younger adults aged 15–59 years (n = 4906, 44.7%) was the highest among the four age groups, followed by older children aged 5–14 years (n = 3432, 31.3%). Young children (0–4 years) and older adults (60+ years) accounted for 18.4% (n = 2020) and 5.6% (n = 619) of the total patients, respectively.

Specimens were collected continuously throughout the study period, with an average of 35.2 specimens collected per week. The sampling volume was slightly lower in the first surveillance year (n = 962, 8.8%), but remained stable in the following 5 years (Table 1).

Prevalence of seasonal influenza among different age groups

Of the patients enrolled, 21.7% (2,385/10,977) were positive for influenza. The overall influenza positivity rate was highest among

Table 1
Demographic characteristics of ILI patients, Pudong New Area, Shanghai, 2012–2018.

Variables		Overall N = 10 977	Age groups (years)			
			0–4 n = 2020	5–14 n = 3432	15–59 n = 4906	≥60 n = 619
Sex, n (%)	Female	5451 (49.7)	948 (46.9)	1656 (48.3)	2462 (50.2)	385 (62.2)
	Male	5526 (50.3)	1072 (53.2)	1776 (51.8)	2444 (49.8)	234 (37.8)
Surveillance year, n (%)	2012–2013	962 (8.8)	170 (8.4)	221 (6.4)	528 (10.8)	43 (7.0)
	2013–2014	1558 (14.2)	313 (15.5)	507 (14.8)	667 (13.6)	71 (11.5)
	2014–2015	2032 (18.5)	448 (22.3)	607 (17.7)	865 (17.6)	112 (18.1)
	2015–2016	2083 (19.0)	386 (19.1)	624 (18.2)	920 (18.8)	153 (24.7)
	2016–2017	2149 (19.6)	317 (15.7)	762 (22.2)	940 (19.2)	130 (21.0)
	2017–2018	2193 (20.0)	386 (19.1)	711 (20.7)	986 (20.1)	110 (17.8)

ILI, influenza-like illness.

Table 2
Influenza virus by subtype/lineage among different age groups in Pudong New Area, Shanghai, 2012–2018.

Type/subtype/lineage	Overall N = 10 977	Age groups (years)			
		0–4 n = 2020	5–14 n = 3432	15–59 n = 4906	≥60 n = 619
Influenza virus, n (%)	2385 (21.7)	191 (9.5)	630 (18.4)	1375 (28.0)	189 (30.5)
Influenza A, n (%)	1794 (16.3)	152 (7.5)	402 (11.7)	1089 (22.2)	151 (24.4)
A/H1N1	424 (3.9)	43 (2.1)	69 (2.0)	284 (5.8)	28 (4.5)
A/H3N2	1370 (12.5)	109 (5.4)	333 (9.7)	805 (16.4)	123 (19.9)
Influenza B, n (%)	591 (5.4)	39 (1.9)	228 (6.6)	286 (5.8)	38 (6.1)
B/Victoria	224 (2.0)	16 (0.8)	97 (2.8)	108 (2.2)	3 (0.5)
B/Yamagata	367 (3.3)	23 (1.1)	131 (3.8)	178 (3.6)	35 (5.7)

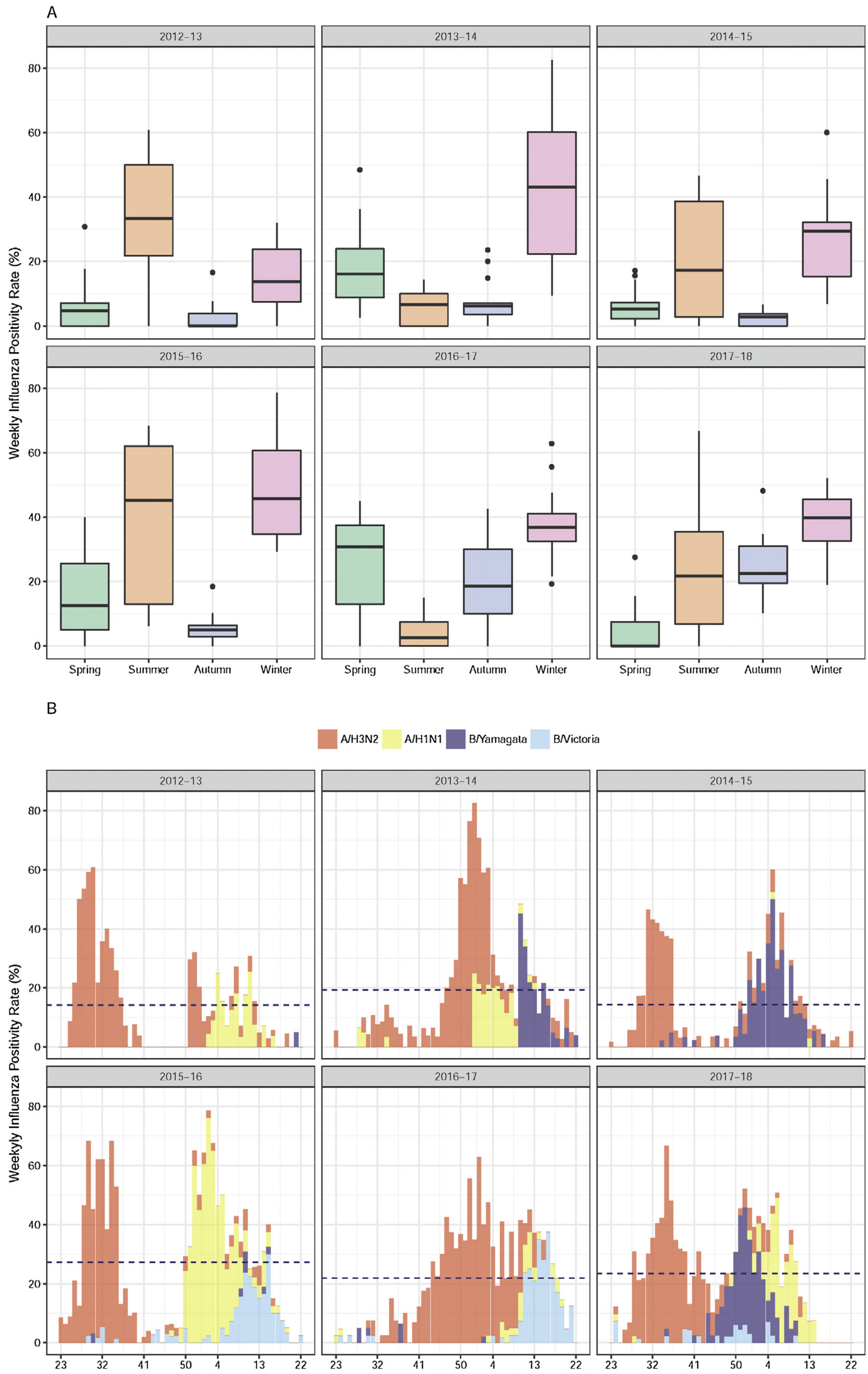

Figure 2. Influenza activity in Pudong New Area, Shanghai, 2012–2018. (A) Positive proportion of influenza virus by season, Pudong New Area, Shanghai, 2012–2018. (B) Seasonal activity of influenza viruses by subtype/lineage in different surveillance years, Pudong, Shanghai, 2012–2018 (the dashed line indicates the annual average weekly influenza positivity rate).

older adults (30.5%), followed by younger adults (28.0%), older children (18.4%), and young children (9.5%, $p < 0.001$). Compared to influenza A ($n = 1794$, 16.3%), influenza B ($n = 591$, 5.4%) was less frequently detected in the whole population ($p < 0.001$). A/H3N2 ($n = 1370$, 12.5%) was the predominant pathogen among the entire study population and each age group. The highest positivity rate of A/H1N1 was found among younger adults (15–59 years) ($p < 0.001$). Compared with the other pathogens, A/H3N2 and B/Yamagata were both more frequently detected among older adults. In contrast, the positivity rate for B/Victoria infection in the elderly group was the lowest (0.5%); B/Victoria was more frequently detected among older children (2.8%, $p < 0.001$) (Table 2).

Seasonal distribution of the overall influenza positivity rate

The influenza positivity rate differed significantly by year ($p < 0.001$). The highest influenza positivity rate was found in 2015/16 (27.0%, 562/2083), followed by 2017/18 (23.8%, 522/2193) and 2016/17 (23.4%, 502/2149). It was relatively lower in 2013/14 (20.7%, 323/1558) and 2014/15 (16.0%, 325/2,032), and it was lowest in 2012/13 (15.7%, 151/962). Overall, among the four seasons, the influenza activity level was highest in the winter (37.1%, 1027/2768) throughout the study period, followed by summer (21.8%, 612/2808). In most of the surveillance years (five of the six), the influenza positivity rate peaked in the winter (37.1%, 1027/2768); the exception was in 2012/13, when the influenza positivity rate peaked in the summer (33.7%, 87/258), with a value more than twice the influenza positivity rate in the winter of the same year (15.6%, 33/212, $p < 0.001$). In the five years with winter influenza peaks, the secondary active season varied. In the two surveillance years of 2014/15 and 2015/16, influenza was more frequently detected in summer than in spring or autumn. The difference between the influenza positivity rate in summer (39.8%) and that in winter (44.4%) in 2015/16 was not significant ($p = 0.4$). In addition to summer, spring was also found to be a secondary influenza season in 2013/14 and 2016/17, with influenza positivity rate values of 17.3% and 27.1%, respectively. In the last surveillance year of this study (2017/18), autumn was the secondary influenza season (25.7%, 135/526; Figure 2A).

Characteristics of seasonal influenza epidemics by subtype

Semiannual epidemics in winter/spring and summer were found in three of the six years during the surveillance period, while in the other three years, only one annual epidemic was identified. The annual epidemic occurred in the winter/spring season in 2013/14 and 2016/17 and in the summer season in 2012/13. The annual winter/spring epidemic usually started in week 50 (the middle of December) and ended around week 15 (early April). In 2013/14 and 2016/17, when there were no summer epidemics, the annual epidemics started earlier (weeks 44 and 47, respectively). The durations of the winter/spring epidemics in 2013/14 and 2016/17 were 19 weeks and 28 weeks, respectively. Compared to the duration of the winter/spring epidemics in the other three years (12, 14, and 19 weeks), the epidemics in 2013/14 and 2016/17 were significantly longer ($p < 0.001$). The average initial week of the four summer epidemics was week 29.5, and the epidemics usually lasted for 8–12 weeks, differing by year. A/H3N2 was the predominant pathogen in each summer epidemic and in the two winter/spring epidemics in the years that lacked summer epidemics. The other three winter epidemics, however, were dominated by A/H1N1 (2015/16) and B/Yamagata (2015/16, 2017/18) (Table 3; Figure 2B).

Different predominant pathogens were observed during the winter/spring epidemics in this study. In 2013/14, 2015/16, and 2016/17, influenza A (A/H3N2 or A/H1N1) led to the beginning of winter/spring epidemics, while the influenza B percentage increased at the end of winter and extended the epidemic to the middle of spring. The heat map of influenza virus activity during the 6 years of this study indicates the most frequent periods for each subtype/lineage (Figure 3).

Seasonality decomposition analysis

Time-series seasonal decomposition analysis demonstrated a semiannual cycle of overall influenza activity during the study period. The summer epidemic was caused by the peak of A/H3N2, and the winter epidemic was prolonged by influenza B into the spring. The long-term trend suggested that after excluding seasonal influence, two lineages of influenza B were active in alternate years (Figure 4).

Discussion

Main findings

This study is novel in revealing the seasonality of influenza viruses by subtype and lineage in eastern China after the 2009 A/H1N1 pandemic. The study highlights the complexity of influenza activity in this area. Co-circulation of A/H3N2, A/H1N1, and two lineages of influenza B contributed to the annual winter epidemics,

Table 3
Characteristics of seasonal influenza virus epidemics in Pudong New Area, Shanghai, 2012–2018.

Characteristics	Surveillance year					
	2012/13 season	2013/14 season	2014/15 season	2015/16 season	2016/17 season	2017/18 season
Epidemic periodicity	Annual	Annual	Semiannual	Semiannual	Annual	Semiannual
Winter/spring epidemic period	–	2013/11/17–2014/4/6	2014/12/28–2015/3/8	2015/12/6–2016/4/3	2016/10/23–2017/4/30	2017/12/10–2018/3/4
Start time (week number)		47	53	50	44	50
End time (week number)		15	11	15	18	10
Duration (number of weeks)		19	12	19	28	14
Predominant subtype/lineage		A/H3N2; A/H1N1; B/Yamagata	B/Yamagata	A/H1N1; B/Victoria	A/H3N2; B/Victoria	B/Yamagata; A/H1N1
Summer epidemic period	2012/6/24–2012/9/2	–	2014/7/14–2014/8/31	2015/7/5–2015/8/23	–	2017/7/30–2017/10/15
Start time (week number)	26		29	28		31
End time (week number)	36		36	35		42
Duration (number of weeks)	11		8	8		12
Predominant subtype/lineage	A/H3N2		A/H3N2	A/H3N2		A/H3N2

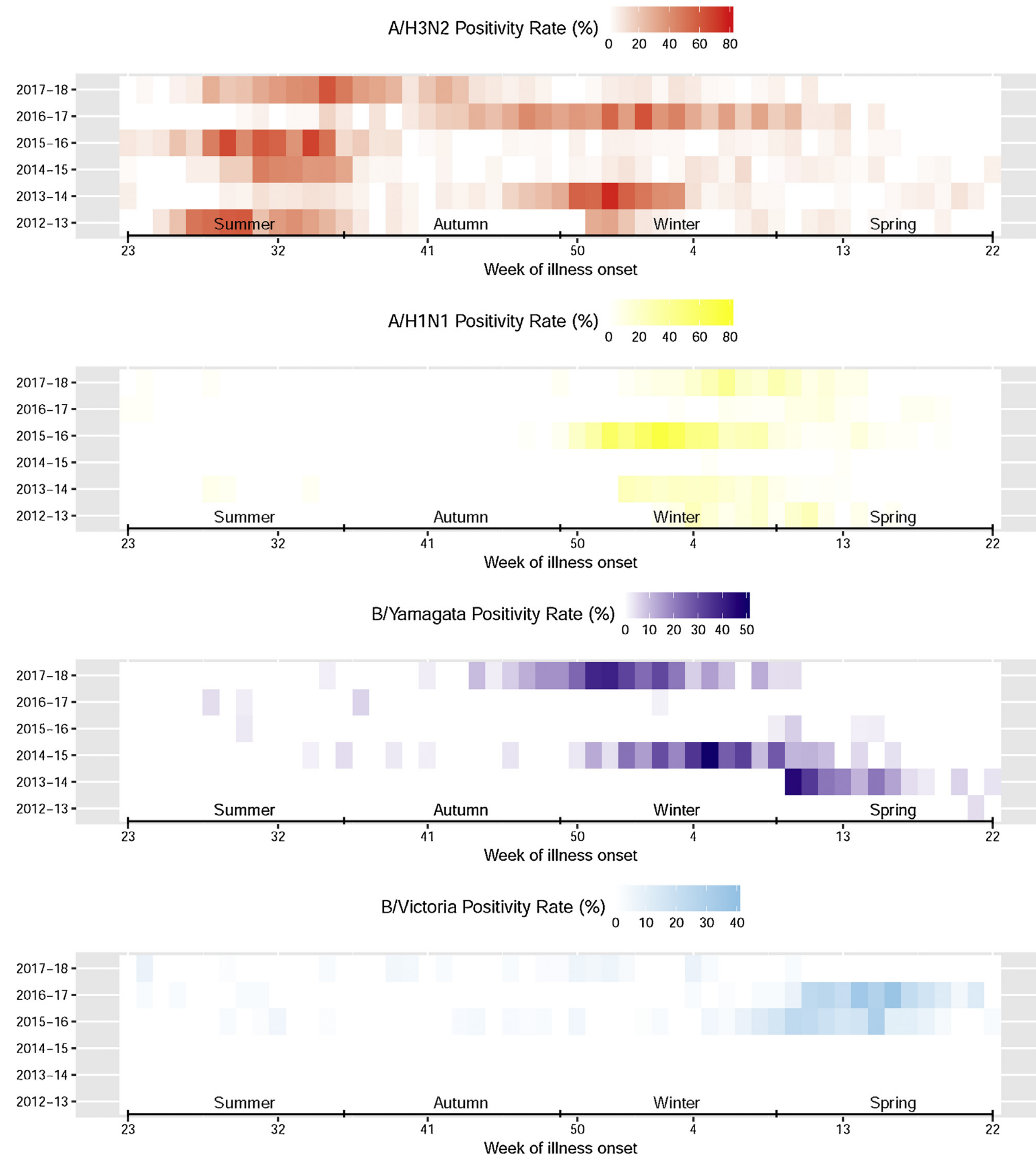

Figure 3. Heat map of influenza virus activity by subtype and lineage in Pudong New Area, Shanghai, 2012–2018.

which lasted into the spring in some years, while the semiannual epidemics in the summer, which were found in four of the 6 years, were only attributable to A/H3N2.

Influenza activity among different age groups

During the study period, the overall influenza positivity rate (21.7%) was highest among older adults (30.5%) and lowest among young children (9.5%, $p < 0.001$). ILI can also be caused by other respiratory pathogens, such as respiratory syncytial virus (RSV) and adenovirus, for which no diagnostic tests were performed in this study. The low influenza positivity rate among children might reflect a higher RSV infection rate in this age group (Lim et al., 2017) rather than a lower influenza infection risk.

Compared to influenza A ($n = 1794$, 16.3%), influenza B ($n = 591$, 5.4%) was less frequently detected ($p < 0.001$). A/H3N2 was predominant in the whole population and among each age group. This is consistent with the influenza surveillance results from other subtropical cities in subtropical China (Qi et al., 2016). The finding of the highest positive proportion of influenza B and B/Victoria among children aged 5–14 years is similar to the result of a current national study in China (Yang et al., 2018a,b). However, a

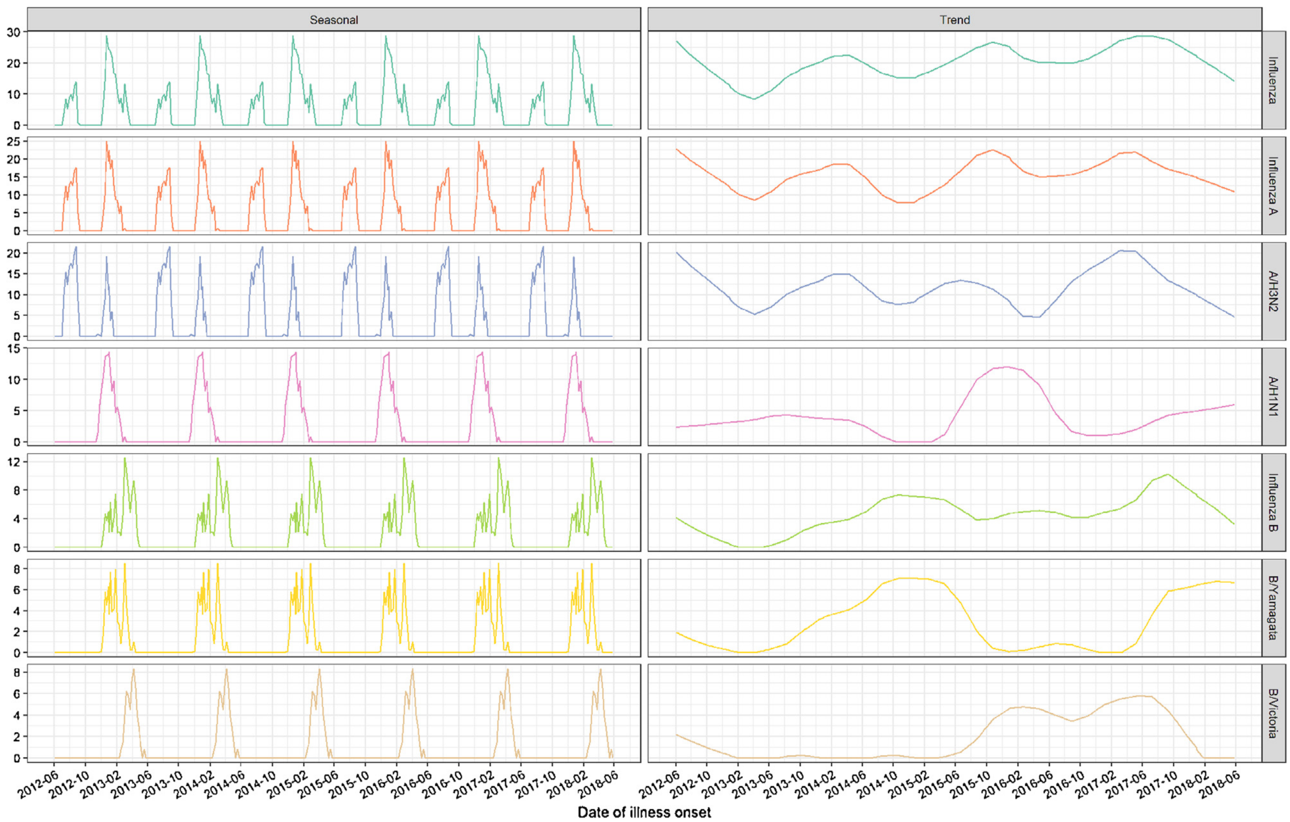

Figure 4. Seasonal decomposition analysis of influenza A and B in Pudong New Area, Shanghai, 2012–2018.

significantly higher B/Yamagata percentage was found in older adults in the present study, which is different from previous results (Caini et al., 2015; Vijaykrishna et al., 2015).

Characteristics of influenza epidemics

For the overall influenza positivity rate, an annual peak in winter/spring was found in most years during the study period, except in 2012/13, when the influenza positivity rate was highest in summer. According to this study, the annual winter/spring epidemics were significantly dominated by influenza B. It is reasonable to assume that the extremely low activity level of influenza B in 2012/13 is the most likely explanation for this exception to the general pattern. This phenomenon was also found in other districts in Shanghai (Zhao et al., 2015) and in other provinces in China that year (Yang et al., 2018a,b).

A semiannual epidemic in the summer was found in this study and has also been reported in other subtropical cities in China (Yang et al., 2018a,b). However, in 2013/14 and 2016/17, this summer epidemic did not occur in Shanghai. A study conducted in Shanghai recently also found the summer epidemic to be missing in the 2013/14 season (Liu et al., 2017b). This finding differs from the pattern observed in most areas of South China (Shu et al., 2010), but is in agreement with the results of an earlier study in Okinawa, Japan, which is another subtropical city near Shanghai. In that study, summer peaks were only observed in four of the 6 years from 2001 to 2007 (Suzuki et al., 2009).

This study also found that in the 2 years without summer epidemics, A/H3N2 presented a higher activity level, leading to an earlier and longer-lasting winter epidemic than in the years with semiannual epidemics. It is believed that this result has not been mentioned in other studies and needs further study, because this could provide information that would be pivotal in optimizing resource allocation, such as antiviral medication and influenza vaccine.

Previously, it was indicated that the mid-latitude area of mainland China experienced semiannual peaks of influenza A in January–February and June–August (Yu et al., 2013). The present study results confirm this pattern and further demonstrate that the summer peak was only attributable to A/H3N2 in Shanghai. The current influenza vaccine that is available in autumn (before November) in the Northern Hemisphere might provide limited protection against the local summer epidemic.

In addition to A/H3N2, the other three subtypes of influenza viruses co-circulated in the winter/spring season, with influenza B occurring later than A/H3N2 and A/H1N1 in most years. This pattern was also confirmed in other regions in the Northern Hemisphere (Baumgartner et al., 2012). The seasonal decomposition analysis indicated that the influenza B peak in the spring occurred later than in other subtropical cities in South China (Qi et al., 2016; Zou et al., 2013) and earlier than in Okinawa, Japan (Iha et al., 2016). Shanghai is an international metropolis with frequent population movements and a very large immigrant population. The present study suggests that the epidemiological pattern of influenza in Shanghai might differ from those in other subtropical cities in mainland China, instead potentially showing more similarity to patterns in other international coastal cities (Hsieh et al., 2005; Iha et al., 2016).

From 2014 to 2018, B/Yamagata and B/Victoria alternated activity annually, which is a pattern that has been described as Z-shaped in some previous studies (Caini et al., 2015; Vijaykrishna et al., 2015).

Influenza vaccination status in Shanghai

The seasonal influenza virus transmission pattern might be significantly affected by the vaccination coverage rate, effectiveness, and scheduling (timing, vaccine type, matching with circulating virus or not), which usually varies by region, age group, and subtype/lineage of influenza virus. Currently, the influenza vaccine is not covered by the national Expanded Program on Immunization in mainland China. It has been estimated previously that the overall influenza vaccination coverage rate is lower than 2% (Feng et al., 2010). The estimated influenza vaccination coverage rate acquired from the vaccination register system in Pudong was about 1.35% among the total population in the 2017/18 season. According to a survey conducted in 2017, the influenza vaccination coverage rate among older adults in Pudong New Area was 5.2% in the 2016/17 season (Ye et al., 2018), which is markedly lower than rates in most developed and developing areas around the world.

On the other hand, influenza vaccine is only available annually between autumn (October or November) and winter (February of the next year) in Shanghai. Considering that the time lag of the anti-influenza virus response reaches a peak and then declines post-vaccination (Cox et al., 1994; Cate et al., 1983), even if the coverage rate was high enough, it might only provide limited protection for the population, especially during those years with summer peaks or earlier winter peaks. In recent years, more specific vaccination schedules have been implemented in other areas with year-round influenza activity. In Hong Kong, influenza vaccine is available from September or October until April to May each year (Feng et al., 2018). Thus, the difference in the influenza virus transmission patterns found between the present study and those conducted in other areas might be the result of both the complex transmission pattern of influenza virus itself and the region-specific herd immunity level, which is influenced by the vaccination situation.

Limitations

The main limitations of this study are the relatively small sample size at the beginning of the surveillance period and the uneven distribution across age groups, with fewer samples from older adults than from individuals in other age groups. It is assumed that this bias had a minimal effect on the study conclusions because the findings were confirmed by the results of other studies, including the unique pattern in the first year and the viral characteristics among the different age groups. In addition, only the positive proportion was used to represent influenza activity. This index might be influenced by the sampling method and healthcare-seeking behavior. However, previous studies comparing the different data sources from the influenza surveillance system in China have shown similar seasonal and transmission patterns of influenza.

Conclusions

This study highlights the complexity of influenza virus activity in a subtropical region of eastern China and suggests that the epidemic features of influenza A and B vary by subtype and year. The current one-season vaccination program in Shanghai, China should be carefully reconsidered.

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Role of the funding source

The funding source of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the article. The corresponding authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

Ethics clearance for this research was given by the Ethics Review Board of Pudong New Area Centers for Disease Control and Prevention (PDCDC). Informed consent was obtained from all patients enrolled. All potentially identifying factors have been removed to prevent the identification of individuals.

Conflict of interest

The authors declare that they have no competing interests.

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