Abstract

Background: Influenza is a disease under surveillance worldwide with different seasonalpatterns in temperate and tropical regions. Previous studies have conducted modeling of influenza seasonality by climate variables. This study aimed to identify potential meteorological factors that are associated with influenza seasonality in Jinan, China.

Methods: Data from three influenza sentinel hospitals andrespectiveclimatefactors (average temperature, relatively humidity, sunshine, accumulated rainfall and speed of wind), from 2013 to 2016, were collected. Statistical and wavelet analyses were used to explore the epidemiological characteristics of influenza virus and its potential association withclimatefactors.

Results: The dynamics of influenza werecharacterized by annual cycle, with remarkable winter epidemic peaks from December to February. Temperature and relative humidity(RH) or atmospheric pressure influenced the seasonality of influenza A(H3N2) virus, whereas atmospheric pressure and temperature or absolute humidity (AH) shaped the seasonality of influenza virus B, and temperature and AH or RH influenced the change of influenza A(H1N1)pdm09. During the epidemic season, the prevalence of influenza virus lagged behind the change of temperature and atmospheric pressure led by 1-8 weeks and 0.25-1.5 weeks for different influenza virus types or subtypes, respectively.

Conclusion: Climate factors were significantly associated with influenza seasonality in Jinan during the influenza epidemic season, and the optional time for influenza

vaccination is before November. These finding ~~may be utilized~~ in influenza control and prevention.

Key words: Influenza surveillance, wavelet analysis, seasonality, climate factors

Introduction

Influenza remains a global public health concern, causing 3-5 million severe illnesses and 291-646 thousand deaths (Iuliano et al., 2018). Influenza epidemics show distinct seasonality pattern, particularly in winter in temperate areas and a more diverse behavior in tropical and subtropical areas, where influenza displays semi-annual or annual epidemic cycles, and year-round activity (Tamerius et al., 2013). However, the durations and transmission of influenza outbreaks vary among periods (Onozuka et al., 2015). Azziz Baumgartner et al (2012) showed that 7 of 47 (15%) temperate countries presented two or three influenza epidemic period every year, and year-round activity in 3 of 43 (7%) temperate countries. Thus, accurately documenting the dynamics of influenza epidemics and understanding its epidemic patterns are of great importance not only to scientific interest, but also public health (Thai PQ et al., 2015).

The seasonality of influenza epidemics is associated with many factors, including virus mutation, people susceptibility, climate, and environmental changes. Among all of the factors, climate plays the most important role in influenza seasonality (Lofgren et al., 2007; Lowen et al., 2014; Tamerius et al., 2011). Experimental studies in guinea pigs showed that the influenza virus is stable at low relative humidity (RH) and relatively unstable at intermediate RH and absolute humidity (AH) impacts the influenza virus viability and transmission. Yang et al. (2012) proposed that the effect of RH on influenza virus stability may be due to changes in salt concentration within droplets. Influenza virus is also more stable at low temperatures, which may be due to an increased virus half-life at low temperatures, decreased activities of proteases, and cooler epithelial surface (Aniceet al. 2014). Furthermore, temperature and RH influence the innate defense of host nasal epithelia and the production of infectious bio-aerosols, thereby shaping influenza seasonality. Some studies have hypothesized that influenza virus stability increases with reduced sun activity (Hope-Simpson, 1981).

To test whether climate factors shape the seasonality of influenza, epidemiological studies comparing influenza seasonality to metrological conditions have been performed, which showed that lower temperature and AH increase influenza virus survival and transmission in temperate regions (Shaman et al., 2009, 2010, 2011).Tamerius et al. (2013) and Bloom-Feshbach et al. (2013) showed that the onset of influenza epidemics is associated with the cold-dry and humid-rainy condition in temperate and tropical areas, respectively. Although influenza patterns have been well described in developed temperate regions, those involving developing temperate areas are limited. Yu et al. (2013) showed that minimum temperature, the hours of sunshine and maximum rainfall are closely related with influenza seasonality in China, but AH was not taken into consideration, and the influenza surveillance data from April-September in northern China was missing. Yang et al. (2019) demonstrated the negative association between the positive rate ofinfluenza virus with temperature and AH in Gansu Province, North of China. Chao et al. (2010) revealed that influenza A(H1N1)pdm09 was negatively correlated to temperature and AH in Beijing. Sun et al. (2018) found a negative relationship between the positive rate of influenza virus and temperature and AH in Beijing. However, studies on the relationship between different influenza virus types or subtypes and climate factors are limited. Therefore, understanding the influence of climate factors is vitally important to learn the influenza seasonality pattern and consequently implement prevention and control strategies.

In this study, we analyzed the seasonality of influenza and explored various climate factors, including AH, RH, temperature, atmosphere, sunshine, wind speed, and accumulated rainfall as potential drivers to the seasonality of laboratory-confirmed influenza cases in Jinan City, the capital of Shandong Province, eastern of China, from 2013 to 2016, which is a temperate city with 7 million people and 3 sentinel hospitals for the surveillance of influenza. This detailed analysis of influenza pattern will provide evidence to foster strategies to prevent and control influenza in different years.

Methods

Influenza surveillance data

Epidemiological and virology data of three national influenza surveillance sentinel hospitals was collected from Jinan Center for Disease Control and Prevention for the study period of 2013–2016, including QiLu Children's Hospital of Shandong University, the No. 4 Hospital of Jinan, and the No. 6 Hospital of Jinan (The People's Hospital of Zhang-QiuArea, Jinan). Influenza surveillance was conducted year-round based on the three sentinel hospitals. For each hospital, at least 20 nasopharyngeal swab specimens were collected each week from patients with influenza-like illness (ILI), which was defined as an outpatient of any age with an acute respiratory infection syndrome with fever ≥38°C and cough or sore throat. All collected samples were tested for influenza virus by virus isolation in Madin-Darby canine kidney cells.

The types [influenza A and B), subtypes (A(H3N2) and A(H1N1)pdm09], and lineages of influenza B (Yamagata and Victoria) were identified by haemagglutination assay and haemagglutination inhibition (HI) test according to National Influenza Surveillance Protocol published by Chinese Health commission of the People's Republic of China. In this study, we chose the weekly positive rate of different influenza virus types or subtypes as influenza virus proxy (Positive rate = Number of positive specimens/Total number of specimens tested per week ×100%) to illustrate the seasonality of influenza according to Tameriu et al. (2011) and Liu et al. (2017).

Climate data

Daily meteorological data from 2013 to 2016 from Jinan were obtained from China Meteorological Science Data Sharing Service System, including weekly average values of temperature (°C), atmospheric pressure (hPa), RH (%), wind speed (m/s), accumulated rainfall (mm), and sunshine duration (h). The weekly average AH (g/m^3) was calculated based on the data of average temperature and RH using the formula described by Xiao et al. (2012).

Statistical methods

First, a descriptive analysis was used to reveal the characteristics of influenza epidemics and climate factors. To characterize the epidemics of influenza virus, continuous wavelet transform (CWT) was applied to illuminate the time frequencies of influenza virus according to the methods described by Cazelles et al. (2007), which has been widely used to explore the temporal and spatial variations of different infectious diseases, including influenza (Xiao et al., 2012; Liu et al., 2017).Wavelet transform can divide the time series into a family of wavelets using dilated and translated functions called "mother wavelets." In this study, a complex wavelet, the

Morlet wavelet was selected as the mother wavelet, which can be well localized in scales and in high-frequency resolution and is regarded as an efficient means of detecting and analyzing the time series (Ng et al. 2012).

Second, to explore the potential relationship between influenza virus and climatic variables, Spearman's correlation was conducted to determine the correlation between different climate factors and influenza types or subtypes.

Third, wavelet coherence analysis was used to investigate thepossible inter-connectedness between influenza virus and climate variables according to the method described by Grinsted et al. (2004). From two CWTs, we performed wavelet coherence analysis (WTC). The WTC shows the significant coherence against red noise in time-frequency space, which can depict the significant covariance at specific periods (frequencies) and phase shift between two time-series.

Last, to exploit the possible relationship, multiple wavelet coherence (MWC) was applied to identify whether the combination of two factors of climate factors correlated with that of the influenza virus. MWC is a technique that is similar to multiple correlations and helps to seek the resulting wavelet coherence of two independent variables on a dependent one at a given time and frequencies (Ng and Chan 2012). The continuous wavelet analysis, wavelet coherence analysis, and MWC were performed using the MATLAB software package downloaded from http://noc.ac.uk/using-science/corsswavelt-wavelet-coherence (version 7.9.0).

Results

Descriptive statistics

Seasonality and periodicity of influenza virus in Jinan

A total of 9170 ILI samples were collected, and 914 laboratory-confirmed cases (9.94%) were identified by virus isolation from 2013 to 2016, including 370 influenza A(H1N1)pdm09, 299 influenza A(H3N2), and 245 influenza B (219B/Yamagata lineage and 26 B/Victoria lineage) (Table 1). Influenza A(H1N1)pdm09 and influenza A(H3N2) were detected from 2013 to 2016, accounting for 73.19% of the total positive influenza virus cases. Figure 1A illuminates the seasonal distribution of different influenza types or subtypes or lineages during the periods, which clearly indicated that influenza viruses had seasonality, with one epidemic peak during the winter season. Figure 1B revealed the wavelet power spectrum of the influenza virus. A high-power spectrum indicated frequency- and time-specific periodicity. Although annual influenza epidemic cycles were identified in the 32–64 week band (2013–2016) with high power, influenza virus showed a distinct epidemic peak with high power in the 8–14- and 0–4-week bands in 2014–2015 and 2014–2016 ($p<0.05$), respectively.

Figure 2 demonstrates the seasonality of influenza virus B and A subtypes in Jinan. Similar to the total influenza activity, influenza virus types or subtypes showed an annual cycle with a peak in winter (Figure 2A) Based on CWT, A(H3N2) exhibit a statistically significant periodicity during 2014-2015 with higher power in the 0-4-week band, and influenza A(H1N1) pdm09 was observed two statistically significant regions in 2015-2016 with higher power in the 0-4 and 8-16-week bands. Influenza virus B exhibited a statistically significant periodicity with three high powers in the 0-4-week band during 2014-2016 and one high power in the 6-24-week band in

2014-2015.

Seasonality and periodicity of climate factor in Jinan

Table 2 showed the average values of weekly climate factors, including atmospheric pressure, temperature, and RH, AH, wind speed, sunshine duration, and accumulated rainfall during the study period. Figure 3demonstratesthe weekly variation inclimate factors with obvious seasonal and periodic characteristics. Atmospheric pressure and influenza positive rate showed similar curves, but average temperature and AH exhibited different variations.

Spearman's correlation

Table 3 shows the relative Spearman's correlation of different influenza virus types or subtypes and climate factors. Spearman's correlation analysis shows that weekly average atmospheric pressure is positively correlated with influenza virus types or subtypes. In contrast, weekly average values of temperature, AH, RH, and accumulated rainfall are negatively associated with influenza virus subtypes. Influenza virus has no correlation with the weekly average wind speed and the weekly average sunshine duration ($p > 0.05$), except for influenza A(H3N2) with the weekly average wind speed. Based on these observations, atmospheric pressure, temperature, AH, RH, accumulated rainfall, and wind speed (only for influenza A(H3N2)) were selected for further analysis.

CWT analysis

The results of cross wavelet analysis of influenza virus and different climate factors are shown in Figures 4–6. Cross wavelet analysis provided information on whether two time series are linearly correlatedor co-moved at a particular time and frequency, i.e., the whiter the color, the higher the correlation. Statistically significant relationships are highlighted by a thick black curve around the significant regions. The cone of influence separates the reliable (white colors) and less reliable (pink colors) regions. The orientation of the arrows represents the lag or lead relationship.

For influenza A (H3N2), the result of cross wavelet analysis shows that influenza A (H3N2) is statistically significantly associated with some climate factors in some periods (Figure 4). For atmospheric pressure, influenza A(H3N2) was significantly correlated at the period of approximately 26-week (2013–2014) ($p < 0.05$), with arrows pointing to the left, indicating that both are negatively correlated during 2013–2014. The most prominent power was observed in the 1–6-week band in 2014, with the right and up arrows, illuminating that the prevalence of influenza virus lags behind the changes of atmospheric pressure by approximately 0.5-1.5weeks. For temperature, influenza A(H3N2) was significantly correlated at the period of approximately 26-week (2013–2014) with the left and down arrows, indicating that the changes of temperature leads the prevalence of influenza virus by eight weeks. For the period of approximately 8–10-week band (2015–2016) ($p<0.05$) with the right and up arrows, the change of temperature leads the prevalence of influenza virus by one week during the period. For RH, we also observed one high-power spectrum in the 8–12-week (2014–2015) with anti-phase, indicating that both are negatively correlated during the period. At the same time, in the 32–64-week timescale, we found a strong, but not statistically significant at the 5% level, correlation during the study period between influenza A(H3N2) and different climatic factors, showing that atmospheric pressure is positively correlated and the other climatic factors except for wind speed were negatively correlated with influenza A(H3N2) on the annual cycle during the periods.

For influenza A(H1N1)pdm09, we also observed a statistically significantly association with atmospheric pressure, temperature, RH, and AH on the short or medium scales. For atmosphere pressure, influenza A(H1N1)pdm09 was significantly correlated at periods of approximately 26-week (2014) and 1–12-week (2013–2014) with the left arrows, showing that both are negatively correlated during 2013–2014. In terms of temperature, in the 26-week band (2013–2014), influenza A (H1N1) pdm09 was negatively correlated with the left arrows. For the periods of 6–10-week in 2015–2016, we observed a negative relationship with the change of temperature leading the prevalence of influenza virus by approximately 2–3 weeks, but for the band of the 6–8- (2013–2014) and 6–12- (2014–2015) week, positive correlations were observed. At the same time, some significant periods of 0–4-week (2014) and 4–6-week (2015–2016) of AH were observed, showing that the change of AH leads the prevalence of influenza virus by 0.25 week and 2–3 weeks during the periods, respectively. For RH, we only observed a statistically significant region in the 8–10-week (2014–2015), with influenza virus leading. Similar to influenza A (H3N2), on the one-year scale, atmosphere pressure was positive and the other climate factors except for rainfall were negative with influenza A(H1N1)pdm09 during the periods.

For influenza virus B, we observed the statistically significantly correlation with atmospheric pressure only in the 4–6-week band (2013–2014), with the change of atmosphere pressure leading the prevalence of influenza virus by 0.25–1 week. Similarly, atmospheric pressure was positively correlated and the other climate factors were negatively correlated with influenza virus B on the one-year scale.

Multiple wavelet coherence analysis

After CWT, temperature, humidity (AH and RH), and atmospheric pressure were involved with MWC analysis. The combined impact of any two of four different climate factors and influenza virus can be analyzed using MWC squared. The plots of MWC of three influenza virus types or subtypes are shown in Figures 7–9. Through MWC by comparing different combinations of the climate factors, the results show that not only the short-term (8–14-week), but also the medium-term (26-week) and the long-term trend relationships or co-movement between climate factors and influenza virus types or subtypes are correlated. In addition, the combination that largely influenced influenza seasonality was also observed. For example, the MWC (influenza A(H3N2)-temperature-RH) plot in Figure 7C shows that three time series are correlated significantly and share the same coherent areas in the 26-week (2013–2016) and in the 6–12-week period (2013–2016), which can best predict the seasonality of influenza A(H3N2).Thus, based on Figures 7–9, we concluded that the combination of atmospheric pressure and temperature or AH, temperature and AH or RH, and RH and atmospheric pressure or temperature were associated with influenza virus B, influenza A(H1N1)pdm09, and influenza A(H3N2), respectively.

Discussion

In this study, we exploited influenza seasonality and the potential relationship between influenza seasonality and different climate factors. Through descriptive analysis and wavelet analysis, we found that influenza virus exhibited an annual epidemic cycle with remarkable winter seasonality in Jinan, and concluded the potential relationships or co-movement of influenza virus types or subtypes and different climate factors were quite correlated in Jinan from 2013 to 2016.

Although influenza-like illness was used to represent the level of influenza activity in some studies (Azziz et al., 2012; Thai et al., 2015; Tamerius et al., 2011), the laboratory-confirmed data is thought to be a better indicator to depict the influenza seasonality (Tamerius et al., 2011; Liu et al., 2017). Thus, in our study, the weekly positive rate of influenza virus was used to precisely illustrate the epidemic and seasonality of influenza virus. The description statistics and CWT analysis indicated that influenza virus had an annual cycle with regular peak seasonality in winter season and was scarce in the summer and autumn seasons in Jinan City, which was in accordance with the findings of previous reports in temperate regions (Wu et al., 2016; Caini et al., 2016, 2017). The CWT analysis further illuminated that the onset of epidemic of influenza virus always began in December and the epidemic peak time could last for 8–14 weeks in every surveillance year (Figure 1B). Unlike other studies that the influenza virus had two or three peaks in a temperate zone (Azziz et al., 2012), we only found an obviously epidemic peak in Jinan. By analyzing the time series of each influenza type or subtype, the descriptive analysis and CWT analysis also illuminated that three influenza viruses were detected every year with one or two influenza virus subtypes predominated in winter, and the predominant influenza virus changed with the years. In the early stage of 2013, influenza A(H1N1) pdm09 was the main epidemic virus. In 2013–2015 surveillance years, influenza virus B and influenza A(H3N2) virus were the main epidemic strains with few influenza A(H1N1)pdm09 detected. In 2015–2016 surveillance year, the predominant virus was changed to influenza A(H1N1)pdm09 and influenza virus A(H3N2) become the predominant virus in the last month of 2016. Therefore, understanding the influenza seasonality suggested that the optional time of influenza vaccination programs was from September to November in Jinan, which provided immune protection in the epidemic peak time. Otherwise, the vaccine effectiveness wanes over time (Kissling et al., et al., 2013; Ebody et al., 2013).

The seasonality of influenza virus indicated ~~the epidemic patterns of influenza viruses~~ with peak in winter and the predominant influenza virus changed during different years. As for the mechanism of the seasonality and alternation of influenza virus subtypes, host susceptibility, virus mutation, and climate factors may have driven influenza virus circulation activity. Therefore, we exploited the potential association between influenza virus subtypes and different climate variables through the CWT analysis and MWC analysis. We speculated weekly change in climate variables significantly contributed to dynamic variation of influenza virus, which was in agreement with the findings of previous studies (Tamerius et al., 2013; Onozuka et al., 2015; Azziz et al., 2012). Through WTC analysis and MWC, we concluded that there were statistically significant associations between atmosphere pressure, temperature, and humidity (RH and AH), and influenza seasonality.

For weekly atmosphere pressure, we observed that there was positive association with three different influenza virus subtypes in the annual cycle, but this relationship varied with week timescales during 2013–2016, which was consistent with the findings of previous studies in avian influenza viruses (Li et al., 2015; Soebiyanto et al., 2010). On the short- and the medium-term, atmospheric pressure influenced the variations in different influenza virus types, which revealed that atmospheric pressure may be a driver of influenza virus. The results were ~~verified~~ by MWC analysis, which was consistent with the results of Sundell et al. (2016). Furthermore, during some time periods, the prevalence of influenza virus lag the changes in atmospheric pressure, which can predict the occurrence of influenza virus A(H3N2) epidemics. It is possible that the higher atmospheric pressure occurred in the winter and was lower in the summer, which was consistent with the occurrence of influenza virus epidemics. The other explanation could be that the mucous membrane of nasal cavity was easily broken in dry conditions and high atmosphere pressure in the winter season, and influenza virus could easily enter the mucous membrane to infect it. However, the detailed mechanism requires further investigation.

Temperature and RH were often reported to be associated with influenza seasonality, especially in warm regions with influenza epidemic peaks in the winter (Yu et al., 2013; Soebiyanto et al., 2010; Tamerius et al., 2019). In Jinan, we also observed a negative association between average temperature and three influenza virus subtypes with CWT and MWC. Except for the negative relationships, we also observed that during some time periods, changes in temperature lead the prevalence of influenza virus A(H1N1)pdm09 and influenza A(H3N2) by 2–3 weeks (2015–2016) and 1 week (2015–2016), respectively. We did not observe any significant correlation between influenza virus B and temperature, but on the one-year scale, the correlation was negative. Therefore, temperature may be a good predictor of influenza virus epidemics, not only influenza virus A, but also influenza virus B. For RH, we observed the negative association with three influenza virus subtypes in different week bands during various periods, and we did not observe any lead correlations with influenza virus. In winter, the dry and cold condition can increase influenza transmission. Lowens et al. (2014) found that the influenza transmission was most efficient at low temperature (5℃) and low RH (20% to 35%), but the transmission and survival capacity declined as temperature increased from 5℃ to 20℃ and was completely blocked at 30℃ based on the study conducted in guinea pigs. In Jinan, the influenza peak always occurred in December–February with mean temperature at -5°C to 5°C, whereas RH was 30%–60%, which increased the influenza transmission.

In the study, we also observed a negative association between AH and influenza virus in the annual cycle. For influenza A(H1N1)pdm09, changes in AH leadtheprevalence by 2–3 weeks and 0.25 weeks during 2015–2016 and 2014, respectively, which revealed that AH was a good predictor of influenza A(H1N1)pdem09. For influenza B, we also observed the potential negative correlation during the 8–12-week during 2013–2014, with the left arrows. MWC analysis further demonstrated that temperature influences the seasonality of influenza virus, which coincided with the experimental results in guinea pig and the epidemiology data analysis (Lowen et al. 2007; Shaman et al., 2007, 2010, 2011; Lowen et al., 2014).

Previous studies have reported that the amount of rainfall increases influenza virus activity in tropical and subtropical areas such as Thailand, French Guiana (Pica et al., 2012; Mahamat et al., 2013). However, in our study, we observed the negative relationship between the accumulated rainfall with influenza A(H3N2) virus and influenza virus B on one-year scales, which is consistent with the findings in Egypt that the infection of H5N1 avian influenza was negatively associated with precipitation between 2006 and 2008 (Monamele et al., 2017; Murray et al., 2011). In Jinan, the rainfall season is mainly concentrated in summer with the average temperature >30℃, and dramatically decreases the half-time of influenza virus and transmission capacity. However, we did not observe the relationship between influenza virus and the sunshine duration in our study, which is different from the study of Yu et al. (2013), in which sunshine duration is a key environmental variable in influenza virus transmission. The reason may be that the accumulation of sunshine duration can influence the duration of influenza virus.

MWC analysis indicated that the combination of any two of four climate factors influenced the seasonality of different influenza virus types or subtypes. Temperature and RH or atmospheric pressure influenced the seasonality of influenza A(H3N2) virus; whereas atmosphericpressure and temperature or AH shaped the seasonality of influenza virus B, andtemperature and AH or RH influenced the change of influenza A(H1N1)pdm09.

Therefore, we conclude that the influenza seasonality may be influenced by some of the relative climate factors, not by one single climatic factor (Tamerius et al. 2011). In 2014–2015 influenza epidemic seasons, atmospheric pressure,temperature, and RH influenced the seasonality of influenza A(H3N2) virus and influenza A(HN1) pdm09; whereas atmospheric pressure, temperature, AH, and RH influenced the seasonality of influenza virus B and influenza A(H1N1) pdm09 in the 2015–2016 influenza epidemic seasons.

Conclusions

In all, based on the wavelet analysis, we elaborated the dynamic variations in influenza virus characterized by annual cycle with remarkable winter seasonality and exploited the potential impacts of climate parameters on influenza virus: temperature and RH or atmosphere pressure influenced the seasonality of influenza A(H3N2) virus; whereas atmosphere pressure and temperature or AH shaped the seasonality of influenza virus B, and temperature and AH or RH influenced the change of influenza A(H1N1)pdm09. Wavelet analysis indicated that changes in different climatic factors lead to different extents of delays in influenza virus occurrence. All of this provides scientific support for influenza virus prevention and control.

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