Association between multiple meteorological variables and seasonal influenza A and B virus transmission in Macau

HoiMan Ng, Yusi Li, Teng Zhang, Yiping Lu, ChioHang Wong, Jinliang Ni, Qi Zhao

Abstract

Few studies have evaluated the influence of meteorological variables on different influenza types in subtropical regions. This study aimed to explore the association between meteorological variables and the onset of influenza A (Flu-A) and B (Flu-B) in Macau. Daily influenza case data in Macau were collected from Kiang Wu Hospital from 1 January, 2014 to 31 December, 2018. Daily meteorological data were obtained from the Macau Meteorological Service. The distributed lag non-linear model (DLNM) was used to estimate the effects of meteorological variables on seasonal influenza outbreaks. Regarding mean air temperature (temp), the peaks of the cumulative relative risks (RRs) of Flu-A and Flu-B were both at 4.0 °C and 28.0 °C. Regarding the diurnal temperature range (DTR), the peaks of the cumulative RR of Flu-A were at 1.0 °C and 5.0 °C, while the cumulative RR of Flu-B increased as the DTR decreased. The association between influenza risks and relative humidity (RH) showed a U-shape curve. The risk of influenza increased when the RH was below 50% or above 90%. The risk of both types of influenza increased significantly when the sunshine duration (SD) was below 3.5 h. Taking the median value as the reference, a significant cold effect was observed over 16–24 days lag for Flu-A. Lag effects were found for both types of influenza in low-DTR, and humid and short SD conditions. This study revealed complex non-linear association between meteorological variables and the different influenza types in Macau.

1. Introduction

Around half a million people die from influenza worldwide annually, which places a considerable disease burden on society (Brody, 2019). There are 4 types of influenza viruses, and Flu-A and B viruses cause seasonal flu epidemics. Flu-A is the most common seasonal virus followed by Flu-B. The transmission patterns of seasonal influenza might be influenced by the complex interaction among influenza viruses, meteorological variables, air pollutants, host susceptibility and human activity patterns (Landguth et al., 2020; Xu et al., 2020; Zhang et al., 2020).

Influenza epidemics show a typical seasonality in temperate regions, where a peak occurs in winter, yet epidemics might occur at different times of the year or all-year-round in tropical and subtropical regions (Tamerius et al., 2013). These varied prevalence patterns might result from the different characteristics of meteorological variables in temperate and subtropical regions. A study conducted in 6 temperate European countries indicated that outbreaks of influenza were strongly associated with low temp (−1.9 °C) and low UV indexes (0.7) (Janevski et al., 2019). Humidity, wind velocity (WV) and atmospheric pressure (atm) showed a low correlation with the peaks of influenza activity (Janevski et al., 2019). A study conducted in Japan found that at the 10th and 25th percentile of temp, the risk of influenza increased in over 65% of prefectures compared with the median value of temp (Chong et al., 2020a,b). At the 10th and 25th percentile of RH, around 40% of the prefectures’ influenza risks were increased when compared with the median value of RH (Chong et al., 2020). Limited research has been conducted in subtropical regions and the results were inconsistent (Chong et al., 2015; Guo et al., 2019; Ma et al., 2021). Hongkong, Guangzhou and Shenzhen are 3 cities located the southern coast of China, which have a subtropical monsoon climate. Rainfall was

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**ABSTRACT**

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Influenza epidemics show a typical seasonality in temperate regions, where a peak occurs in winter, yet epidemics might occur at different times of the year or all-year-round in tropical and subtropical regions (Tamerius et al., 2013). These varied prevalence patterns might result from the different characteristics of meteorological variables in temperate and subtropical regions. A study conducted in 6 temperate European countries indicated that outbreaks of influenza were strongly associated with low temp (−1.9 °C) and low UV indexes (0.7) (Janevski et al., 2019). Humidity, wind velocity (WV) and atmospheric pressure (atm) showed a low correlation with the peaks of influenza activity (Janevski et al., 2019). A study conducted in Japan found that at the 10th and 25th percentile of temp, the risk of influenza increased in over 65% of prefectures compared with the median value of temp (Chong et al., 2020a,b). At the 10th and 25th percentile of RH, around 40% of the prefectures’ influenza risks were increased when compared with the median value of RH (Chong et al., 2020). Limited research has been conducted in subtropical regions and the results were inconsistent (Chong et al., 2015; Guo et al., 2019; Ma et al., 2021). Hongkong, Guangzhou and Shenzhen are 3 cities located the southern coast of China, which have a subtropical monsoon climate. Rainfall was
positively associated with influenza activity in Hong Kong, but the association was not found in Guangzhou or Shenzhen (Chong et al., 2015; Guo et al., 2019; Ma et al., 2021). A moderate WV (2–3 m/s) was considered a risk factor for influenza activity in Shenzhen but in Guangzhou (Guo et al., 2019; Ma et al., 2021). In addition, meteorological variables might have different effects on different influenza types, but research was limited. A study of 8 temperate regions, 2 subtropical regions and one tropical region showed a U-shaped association between temp and Flu-A (Chong et al., 2020). Absolute humidity was negatively correlated with Flu-B virus in temperate regions, whereas absolute humidity was positively correlated with Flu-A and B viruses in subtropical and tropical regions (Chong et al., 2020). Another study conducted in Shanghai, a subtropical city on the east coast of China, found that exposure to a large DTR significantly increased the risk of Flu-A transmission, but the relationship was contrasted in Flu-B (Zhang et al., 2020). Thus, it is necessary to specifically evaluate the association between meteorological variables and different types of influenza activities depending on location. This study aimed to assess the meteorological variables that have a significant impact on different types of seasonal influenza and the extreme effect of meteorological variables on each influenza type in Macau.

2. Material and methods

2.1. Study area

This study was conducted in Macau, located along the southeast coast of China. Macau is one of the most famous tourist cities with around 320 million tourists per year, and is the most densely populated area in the world with 20,426 persons/km². Macau has an oceanic subtropical monsoon climate with an annual temp of 22.8 °C, an annual RH of 78.8%, a total annual SD of 1,773.9 h and an annual WV of 3.7 m/s. In winter, it has a dry and cold climate. In summer, Macau experiences rainy seasons with many typhoons and heavy rains. The seasonal interchannel period between spring and autumn is short (DSMG, 2022). Vaccination of seasonal influenza has been included in the immunization program of the Government of Macau Special Administrative Region. Macau has an influenza vaccination coverage rate of around 24%.

2.3. Data collection

Daily data of Flu A and Flu B cases from Macau were collected from Kiang Wu Hospital from 1 January 2014 to 31 December 2018. Patients with flu-like symptoms who tested positive to influenza virus on throat and/or nasal swabs were considered confirmed influenza cases. Influenza-like symptoms were defined as acute respiratory infection and fever (>38 °C) with one of the following respiratory symptoms including cough, sore throat, or running or congested nose, and one of the systemic symptoms including headache, muscle ache, sweats or chills, or tiredness (Butler et al., 2020). Diagnosis of influenza virus was performed using the BD Veritor system for rapid detection of Flu A/B reagent. Daily meteorological data included: temp, RH, WV, atm, and SD, and these were obtained from the Macau Meteorological Service. Further, the daily maximum and minimum temp were collected to calculate DTR (DTR = maximum temperature – minimum temperature).

2.3. Statistical analysis

A descriptive analysis was used to present the characteristics of the daily meteorological variables and influenza cases. The distribution patterns of influenza cases and daily meteorological variables over time were displayed using scatter plots. The association of daily influenza cases and meteorological variables was examined using Spearman correlation analysis. To evaluate the potential nonlinear impacts of meteorological variables on seasonal influenza transmission with the lag effects of meteorological variables, DLNM was used for Flu-A and Flu-B (Wood, 2006; Gasparini et al., 2010). Then, Spearman correlation coefficients were calculated to explore whether multicollinearity was present between meteorological variables. Only 1 of the highly-correlated meteorological variables (r > 0.8) was included in the model. Due to the strong correlation between temp and atm, the latter was eliminated from the model (Table 2).

2.4. Distributed lag non-linear model (DLNM)

The model was formulated as follows:

\[
\log(E(Y_t)) = \alpha + \beta_1(M, \text{lag, df}) + \sum \text{ns}(X_j, \text{df}) + \text{factor(DOW)} + \text{factor(holiday)} + \text{ns(time, df} \times 5) \tag{1}
\]

where \(E(Y_t)\) is the expected daily count of influenza cases on day \(t\); \(\alpha\) is the intercept; \(\beta_1\) (climate variables) represents the cross-basis matrix of meteorological factor; and \text{ns}() is a natural cubic spline function. \text{Day of the week} (DOW) is included in the model adjusting for day of the week effects. \text{Holiday} refers to a binary variable for public holiday to control for the impact of public holidays. \text{Time} refers to seasonality and long-term trends in influenza and it was found that using a \text{ns} with 7 degree of freedom (df) per year fitted the model best as shown by a previous study (Thomas, 1994). \(M\) represents the meteorological factor analyzed in the cross-basis matrix. \(X_j\) represents other meteorological variables excluding \(M\).

The model was used for each meteorological variable including temp, DTR, RH, and SD. The maximum lag day was defined as 27 days, which was based on the incubation period of influenza and potential lagged effects revealed by previous studies (Guo et al., 2019; Qi et al., 2021). Akaike information criterion (AIC) was used to select the dfs for the meteorological variable in each model and the lowest AIC score was the most fitted model. The AIC values are summarized in Table S1. The effects of temp, DTR, RH and SD were controlled for using 5df, 5df, 4df, and 4df, respectively in the Flu-A model. In the Flu-B model, 5df, 2df, 4df and 3df, respectively, were selected for these variables. The mean/median values of temp, the median values of RH, SD, and the 75th percentiles value of DTR were considered as reference values. Further, we compared the 97.5th percentiles and 2.5th percentiles with the median values to explore the extreme effects of meteorological variables on the onset of influenza. We calculated the RR and 95% confidence intervals (CI) to evaluate the associations. The robustness of the models was tested by performing a sensitivity analysis using 2–5 df for each meteorological variable.

The software R studio 3.6.2 was used for the data analysis, and DLNMs analysis was conducted using the “dlnm” package. A p-value below 0.05 was considered statistically significant.

3. Results

3.1. Descriptive statistics

A total of 17104 influenza cases were confirmed from 1 January 2014 to 31 December 2018. A total of 11,982 specimens (70.1%) were detected as Flu-A, and 5122 (29.9%) were detected as Flu-B. Table 1 shows the daily meteorological conditions and influenza cases. Flu-A had a higher daily incidence than Flu-B with mean numbers of cases of 6.6 and 2.8, respectively. Moreover, the daily medians for Flu-A and Flu-B cases were 3.0 and 0, respectively. The medians of daily temp, DTR, RH, WV, atm and SD were 18.4 °C, 4.0 °C, 77.0%, 2.2 m/s, 1008.0 hPa and 4.5 h, respectively. The time-series distributions of daily Flu-A, Flu-B, and meteorological variables are displayed in Figure 1. For Flu-A, the prevalence during summer and winter was higher than that during other seasons. For Flu-B, there was an increasing trend by years and a seasonal pattern was observed with peaks during spring each year. All meteorological variables maintained a cyclical change from year to year.
Table 1. Statistics of daily meteorological parameters and influenza cases in Macau, 2014–2018.

| Variables      | Mean     | Std. | Min. | P25  | P50  | P75  | Max. |
|----------------|----------|------|------|------|------|------|------|
| Flu-A frequency| 6.6      | 9.6  | 0    | 1.0  | 3.0  | 8.0  | 85.0 |
| Flu-B frequency| 2.8      | 7.0  | 0    | 0    | 0    | 2.0  | 57.0 |
| temp (°C)      | 22.9     | 5.5  | 3.6  | 18.4 | 24.2 | 27.8 | 32.6 |
| DTR (°C)       | 5.4      | 1.9  | 0.90 | 4.0  | 5.5  | 6.7  | 13.0 |
| RH (%)         | 82.0     | 10.7 | 35.0 | 77.0 | 84.0 | 90.0 | 100.0|
| WV (m/s)       | 3.0      | 1.3  | 0.6  | 2.2  | 2.8  | 3.6  | 13.3 |
| atm (hPa)      | 1013.0   | 6.7  | 988.0| 1008.0| 1013.0| 1018.0| 1035.0|
| SD (hours)     | 4.7      | 4.0  | 0    | 0.2  | 4.5  | 8.7  | 12.7 |

Sd: standard deviation; Min.: minimum; Max.: maximum; P25: the 25th percentile; P50: the 50th percentile; P75: the 75th percentile.

Table 2. Spearman correlation between influenza cases and meteorological variables in Macau, 2014–2018.

| Variables      | Influenza A frequency | Influenza B frequency | temp (°C) | DTR (°C) | RH (%) | WV (m/s) | atm (hPa) |
|----------------|-----------------------|-----------------------|-----------|----------|--------|----------|-----------|
| Flu-A frequency| 1                     | 0.47                  |           |          |        |          |           |
| temp (°C)      | –0.19*                | –0.24*                |           |          |        |          |           |
| DTR (°C)       | –0.05*                | –0.10*                | 0.08*     | 1        |        |          |           |
| RH (%)         | 0.06*                 | 0.11*                 | 0.07*     | –0.56*   | 1      |          |           |
| WV (m/s)       | –0.03                 | –0.03                 | –0.43*    | –0.14*   | –0.23* | 1        |           |
| atm (hPa)      | 0.09*                 | 0.15*                 | –0.86*    | 0.05*    | –0.33* | 0.40*    | 1         |
| SD (h)         | –0.09*                | –0.12*                | 0.45*     | 0.56*    | –0.56* | –0.19*   | –0.16*    |

* P < 0.05.

3.2. Correlation analysis

Table 2 demonstrates bivariate correlations between influenza types and meteorological variables. Flu-A and Flu-B were both negatively associated with temp, DTR, and SD and positively associated with RH, and atm. No significant association between either type and WV was found. Statistically significant variables including temp, DTR, RH and SD were used for subsequent analysis.

3.3. Association between meteorological variables and different seasonal influenza types

DLNM showed apparent nonlinear cumulative associations between meteorological variables and the outbreaks of Flu-A and Flu-B (Figure 2).

The results of the highest cumulative RR for Flu-A/Flu-B activity and meteorological variables are shown in Table S2. In terms of temp, the cumulative RRs peaked at 4.0°C for both virus types. At 4.0°C, the cumulative RR of Flu-A was 13.32 (95% CI: 3.57–49.71), and the cumulative RR of Flu-B was 5.57 (95% CI: 1.07–19.43). At 28.0°C, the cumulative RR of Flu-A was 2.40 (95% CI: 1.17–4.91), and the cumulative RR of Flu-B was 3.83 (95% CI: 1.50–9.80). At 20.0°C, another peak of the cumulative RR was found for Flu-B only with 3.53 (95% CI: 1.16–10.78). For DTR, the cumulative RR of Flu-A peaked at 1.0°C (RR: 4.89, 95% CI: 1.05–22.76) and at 5.0°C (RR: 3.95, 95% CI: 2.15–7.25). The cumulative RR of Flu-B increased as the DTR decreased and it peaked at 1.0°C (RR: 2.58, 95% CI: 1.41–4.73). The association between the risk of each influenza type and RH were similar and showed a U-shape curve. The first peak of the cumulative RR of Flu-A and Flu-B was at 35%, with 18.43 (95% CI: 10.60–32.07) and 4.95 (95% CI: 2.63–9.31), respectively. As the increasing of the SD, another peak of the risk of both types was observed at 9.0 h with 9.02 (95% CI: 4.75–17.13) and 4.28 (95% CI: 2.45–7.48).

The lagged association between meteorological variables at specific values, which are the highest points in Figure 2, and Flu-A/Flu-B were then analyzed. For temp, the highest risk of Flu-A at 4.0°C was found at the lag of day 7 (RR: 1.24, 95% CI: 1.15–1.33). The highest risk of Flu-B at 4.0°C was found at the lag of day 7 (RR: 1.14, 95% CI: 1.05–1.23), day 21 (RR: 1.14, 95% CI: 1.05–1.23) and day 27 (RR: 1.14, 95% CI: 1.05–1.23). The lagged effect of 4.0°C on Flu-B continued from the day 7 to day 27 lag. In terms of DTR, 1.0°C exhibited the highest risk of Flu-A at the day 21 lag (RR: 1.22, 95% CI: 1.13–1.33), and the highest risk of Flu-B at the day 27 lag (RR: 1.18, 95% CI: 1.03–1.35). An RH of 35% at the day 7 lag showed the highest risks for both types of influenza, with RRs of 1.17 (95% CI: 1.08–1.26) for Flu-A and 1.13 (95% CI: 1.03–1.26) for Flu-B. Moreover, the lowest SD of 0 h had the highest risks of Flu-A at the day 7 lag (RR: 1.14, 95% CI: 1.10–1.17) and Flu-B at the day 27 lag (RR: 1.09, 95% CI: 1.01–1.17). The detailed RRs with 95% CI by time lag are shown in Table 3, and the trends of lag-response curves of each influenza type are displayed in Figure S1.

The trends of lag-response curves of extreme effects of the meteorological variables on Flu-A and Flu-B are displayed in Figures 3 and 4. For Flu-A, a significant cold temp effect was observed along the day 16–24 lag, and the hot temp effect was not significant. No extreme effects of temp were found for Flu-B. Only low-DTR effects but no high-DTR effects were found for Flu-A and Flu-B. The low-DTR effect appeared within the day 21–27 lag of Flu-A, and within the day 2–14 lag and the day 24–27 lag of Flu-B. The humid, but not the dry, weather effect was significant for both Flu-A and Flu-B. A significant humid effect was found within the day 6–27 lag for Flu-A and within the day 6–13 lag and the day 24–27 lag for Flu-B. Short SD was a significant risk factor for the day 1–27 lag for Flu-A and the day 4–27 lag for Flu-B, while long SD was not significant for either influenza types. Table S3 shows the detailed RRs with 95% CIs by time lag of extreme effects of the meteorological variables on Flu-A and Flu-B.
Figure 1. Daily distribution of Flu-A, Flu-B and meteorological variables in Macau from January 2014 to December 2018.

Figure 2. The adjusted cumulative association between meteorological variables with Flu-A and Flu-B using DLNMs in Macau from January 2014 to December 2018. Note: For the Flu-A model, the temp reference value is the mean. For the Flu-B model, the temp reference value is the median. In both models, the DTR reference value is the 75th percentile value, and RH and SD reference values are the medians. The results were adjusted by day of the week effect, holidays and seasonality.
4. Discussion

In this study, it was found that temp, DTR, RH and SD were significantly associated with Flu-A and Flu-B based on different time lags which were similar to previous studies conducted in neighboring cities (Zhang et al., 2020; Ma et al., 2021; Qi et al., 2021).

Flu-A virus was the dominant type. It might be because of a faster rate of influenza A virus mutation ranging from around $1 \times 10^{-3}$ to $8 \times 10^{-3}$ substitutions per site per year, which decreases the effectiveness of the vaccination (Taubenberger and Kash, 2010). For Flu-A, the prevalence of Flu-A was higher in Macau in summer and winter compared with the other seasons. For Flu-B, there was an increasing trend over the years, and it exhibited a typical seasonality with the peak at spring each year. The prevalence pattern of Flu-A in Macau was very similar to that of Flu-A in other subtropical cities in China (Yang et al., 2018; Ye et al., 2019; Ma et al., 2021). Flu-B peaked in winter in Shanghai, which is a subtropical city at mid-latitudes in China, whereas the peak in Macau was found in spring (Ye et al., 2019). Macau is located at a low latitude in China and has shorter winters. The potential explanation is that the latitudes and climate characteristics might have an impact on the transmission of Flu-B (Ma et al., 2021).

In our study, cold weather was associated with higher cumulative risks of influenza activity, which is consistent with previous studies performed in temperate and subtropical areas (Tamerius et al., 2013; Ye et al., 2019; Zhang et al., 2020). Low temp ($\leq 24.2^\circ C$) has been shown to maintain the stability of the influenza virus particle by promoting the ordering of lipids on the viral membrane, which is critical for airborne transmission (Zimmerberg et al., 2008). When the temp reduces to $\geq 5^\circ C$, the mucociliary clearance declines which allows the virus to remain on the upper respiratory mucosa (Lowen et al., 2007). Moreover, people prefer to stay indoors, which increases the contact rate (Cheng et al., 2016). Moderately high temp also increased the influenza activity for both types of influenza, and the results are similar to studies conducted in subtropical regions like Shanghai and Shenzhen, China (Zhang et al.,

| Table 3. The RRs with 95% CI of Flu-A and Flu-B associated with meteorological variables at specific values by different time lags in Macau, from 2014 – 2018. |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | RR              | RR              | RR              | RR              | RR              |
|                | 0-day lag       | 7-day lag       | 14-day lag      | 21-day lag      | 27-day lag      |
| Temp           |                 |                 |                 |                 |                 |
| Flu-A $4.0^\circ C$ vs $24.2^\circ C$ | 0.81 (0.65–1.01) | 1.24 (1.15–1.33)* | 1.10 (1.02–1.18)* | 1.16 (1.08–1.25)* | 1.05 (0.87–1.27) |
| Flu-B $4.0^\circ C$ vs $24.2^\circ C$ | 0.76 (0.61–0.93) | 1.14 (1.05–1.23)* | 1.09 (1.01–1.18)* | 1.14 (1.05–1.23)* | 1.14 (1.05–1.23)* |
| DTR            |                 |                 |                 |                 |                 |
| Flu-A $1.0^\circ C$ vs $10.0^\circ C$ | 1.04 (0.87–1.24) | 1.06 (0.98–1.16) | 1.11 (1.02–1.21)* | 1.22 (1.13–1.33)* | 1.20 (1.04–1.40)* |
| Flu-B $1.0^\circ C$ vs $13.0^\circ C$ | 1.13 (0.95–1.34) | 1.08 (1.01–1.16)* | 1.06 (1.00–1.12) | 1.03 (0.97–1.10) | 1.18 (1.03–1.35)* |
| RH             |                 |                 |                 |                 |                 |
| Flu-A $35.0\%$ vs $84.0\%$ | 1.10 (0.93–1.31) | 1.17 (1.08–1.26)* | 1.14 (1.06–1.23)* | 1.00 (0.93–1.08) | 1.15 (1.00–1.32)* |
| Flu-B $35.0\%$ vs $84.0\%$ | 0.96 (0.81–1.13) | 1.13 (1.03–1.26)* | 1.08 (0.99–1.18) | 1.06 (0.97–1.15) | 1.08 (0.95–1.22) |
| SD             |                 |                 |                 |                 |                 |
| Flu-A $0.0$ h vs $4.5$ h | 1.03 (0.95–1.11) | 1.14 (1.10–1.17)* | 1.12 (1.08–1.15)* | 1.12 (1.08–1.15)* | 1.07 (1.00–1.14)* |
| Flu-B $0.0$ h vs $4.5$ h | 0.99 (0.90–1.08) | 1.05 (1.02–1.09)* | 1.06 (1.03–1.10)* | 1.08 (1.05–1.12) | 1.09 (1.01–1.17)* |

* P < 0.05.
A possible reason is that all these cities are located in subtropical monsoon climate regions, and the high temps and rainy summers provide favorable conditions for the virus spread. In warm, humid climates, water droplets evaporate less, and virus-carrying droplets can easily deposit on surfaces, thus increasing the chance of contact transmission (Lowen and Palese, 2009). Hypersecretion of mucin can increase host susceptibility and research found that mucin production increased under 25 °C and 40% RH, but not at 37 °C and 80% RH (Even-Tzur et al., 2010). No aerosol transmission was observed at any humidity levels when the temperature exceeded 30 °C, which might explain the lowest cumulative risks of influenza activity at such temperatures (Lowen et al., 2008).

In our study, small DTR was negatively associated with influenza outbreaks including Flu-A and Flu-B. The effect of low-DTR had 3 weeks–4 weeks lag in Flu-A, while the low-DTR effect had an impact on Flu-B lasting for 4 weeks. In Shanghai, the Flu-A risk dramatically increases after exposure to large DTR, whereas the risk of Flu-B is higher after exposure to stable temps (Zhang et al., 2020). The mechanism of DTR on influenza has not been elucidated. However, another possible reason is that a large DTR occurs during the seasonal interchange period, and the seasonal interchange period is short in Macau which reduces the large DTR effect on the occurrence of influenza.

Both dry and humid conditions promoted the transmission of influenza, and the humid effect persisted for up to 27 days, which is consistent with a cross-dimensional study in 8 cities in China (Ali et al., 2021). Animal transmission studies using the guinea pig and ferrets models showed that high RH (>60%) and low RH (<40%) kept the influenza virus active in droplets for longer periods of time, yet the virus was inactivated at moderate RH (40%–60%) (Lowen et al., 2008; Lowen and Palese, 2009). In respiratory fluid and human mucus, influenza viruses have been demonstrated high viability when the RH was either below 50% or near 100% (Yang et al., 2012). Research also found that inhalation of dry air caused shedding of guinea pig airway epithelial cilia, epithelial cell shedding, and tracheal inflammation, which led to an impairment of innate antiviral defenses and tissue repair (Erjefalt et al., 1997; Kudo et al., 2019). Disruption of airway epithelial integrity caused by inhalation of dry air might be associated with winter epidemics of certain types of respiratory viral infections (Moriyama et al., 2020). In humid conditions, virus-carrying water droplets are more likely to deposit on surfaces, thus increasing the chance of contact transmission (Lowen and Palese, 2009).

Short SD was found to increase the risk of each influenza type. This finding is similar to that of previous studies (Janevski et al., 2019; Qi et al., 2021). One hypothesis is that the lack of SD reduces the synthesis of melatonin and vitamin D in the body, which in turn decreases human immunity (Dowell, 2001). Melatonin can activate intracellular signaling pathways and transcription factors, thereby inhibiting inflammatory activity (Anderson and Reiter, 2020). Vitamin D reduces the risk of infections by inducing cathelicidins and defensins and reducing concentrations of pro-inflammatory cytokines (Grant et al., 2020). Moreover, in our study, we found that the risk of being infected increased with moderately long SD (5.0 h–9.0 h). The exact mechanism explaining this phenomenon is not known and requires further research.

This study had several strengths. Firstly, this was the first study to explore the complex and delayed relationship between meteorological variables and seasonal influenza in Macau. Secondly, both seasonal influenza types were included in this study, which provided more comprehensive and comparable information of the epidemic characteristics as well as the relationships with meteorological conditions. The study also had several limitations were noted in this study. Firstly, the influenza cases were collected from 1 hospital, which might have caused selection bias. However, Kiang Wu Hospital is 1 of the 2 biggest hospitals in Macau. Thus, our results are still likely to be representative. Secondly, a previous study showed that the associations between meteorological variables and influenza activity vary slightly for different age groups (Guo et al., 2019). To further increase the accuracy of results, further work could explore the association between meteorological variables and influenza activity among different subgroups. Thirdly, air pollutants were not adjusted for in this study which might result in bias. Air pollutants such as PM2.5, PM10, O3, and temp have been found to have a significant interaction effect on diseases (Xu et al., 2013; Chen et al., 2018). Fourthly, Macau is an international tourism city. Influenza cases counted in our study covered both local residents and tourists which might lead to selection bias. However, based on our previous research finding showing that tourists account for only a small percentage of total cases (Flu-A: 7.44%, Flu-B: 6.83%), our results are reliable (Ng et al., 2021).
5. Conclusions

This study revealed that temp, DTR, RH and SD were significant non-linearly associated with Flu-A and Flu-B over different time lags in Macau. For temp, the peaks of the cumulative RR of Flu-A and Flu-B were both at 4.0 °C and 28.0 °C. For DTR, the peaks of the cumulative RR of Flu-A were at 1.0 °C and 5.0 °C, yet the cumulative RR of Flu-B increased as the DTR decreased. The association between the risks of Flu-A/Flu-B and RH both showed a U-shape curve. The risk of influenza increased when the RH was below 50% or above 90%. The risks of both types of influenza increased significantly when the SD was below 3.5 h. A significant cold effect was observed over the day 16–24 lag for Flu-A. The lag effects were found for low-DTR, and humid and short SD conditions for both types of influenza. This finding could help the health department to develop an early warning system based on the understanding of the association between meteorological variables and seasonal influenza. Such an early warning system may lead to decreases in the incidence of influenza and optimize the allocation of medical resources.

Declarations

Author contribution statement

HoiMan Ng: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Performed the experiments; Wrote the paper.

Yusi Li: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jinliang Ni: Conceived and designed the experiments.

Teng Zhang; Yiping Lu: Analyzed and interpreted the data.

ChioHang Wong: Performed the experiments.

Qi Zhao: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1161/j.heelion.2022.e11820.

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