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RESEARCH ARTICLE

Epidemiological Characteristics of Influenza A and B in Macau, 2010–2018

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Abstract

Influenza is one of the major respiratory diseases in humans. Macau is a tourist city with high density of population and special population mobility. The study on the epidemiological characteristics of influenza in Macau should bring great value for preventing influenza in tourist cities like Macau in the world. In this study, we collected a total of 104,874 samples with influenza-like illness (ILI) in Macau from 2010 to 2018. Chi-square test and binary multivariable logistic regression were used to investigate the epidemiological characteristics of influenza A and B in Macau. Among these ILI samples, the overall positive rate is 17.17% for influenza A and 6.97% for influenza B. The epidemics of influenza in three years (i.e., 2012, 2017 and 2018) differ from the remaining years (i.e., normal years). In a normal year, influenza A occurs year-round whereas influenza B is seasonal. Our research shows significant differences in influenza infections between different age groups in normal years. Interestingly, our analysis shows no significant difference between locals and tourists in influenza A and B infection in a normal year, whereas the odds of influenza A in tourists were significantly higher than those in locals in July 2017 and the odds of influenza B in tourists were significantly higher than those in locals in January–February 2012 and January–February 2018. This is possibly attributed by the policy of free vaccination to everyone in Macau. These findings should be valuable for preventing influenza in not only Macau but also the world.

Keywords Influenza · Epidemiology · Chi-square test · Logistic regression · Macau

Introduction

Influenza is a contagious respiratory infection caused by influenza viruses. Influenza A and B are two types of influenza virus which is widespread and prevalent in human. Influenza can lead to 3 to 5 million severe infections and up to 650 000 people die of respiratory diseases linked to seasonal influenza each year (WHO 2017; Iuliano *et al*. 2018). Influenza epidemic patterns differ among temperate, subtropical and tropical regions (Saha *et al*. 2016). In temperate regions, influenza epidemics typically occur during the winter months (Finkelman *et al*. 2007; Tamerius *et al*. 2013), such as from November to March in the Northern Hemisphere and from April to September in the Southern Hemisphere, whereas in subtropical and tropical regions, influenza activity occur year-round or one or two peaks per year (Viboud *et al.* 2006; Moura 2010).

Influenza in Myanmar shows seasonality, and the peak of influenza appears in the rainy season from June to September (Dapat *et al.* 2009; Htwe *et al.* 2019). Similarly, influenza in most American tropical regions occurs between April and September (Durand *et al.* 2016). The positivity rate and number of cases of influenza A in Ethiopia exhibits seasonality, with the peak occurring in November and December (Woyessa *et al.* 2018). Several

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Asian countries near the equator, such as Indonesia, Malaysia, Singapore and Vietnam, have identifiable year-round activity (Saha *et al.* 2014). Some researches in Hong Kong also find that influenza epidemics can occur at any time of the year (Wong *et al.* 2004; Yang *et al.* 2015), and the anti-phase patterns between influenza A/H1N1 and A/H3N2 were found in Hong Kong (Chiu APY *et al.* 2018). Influenza activity appears to coincide with the rainy season in some tropical countries (Shek and Lee 2003; Russell *et al.* 2008), whereas influenza activity occurs year-round without well-defined influenza seasons (Tamerius *et al.* 2013).

Macau is one such area that geographically sited in tropics and has a subtropical climate. Macau is located on the south coast of China, with a population density of 20,500 per square kilometer, making it the most densely populated area in the world. Macau is an export-oriented economy and world-famous tourist city with annual tourist traffic exceeds 35 million. The large influx of visitors can increase the complexity of virus types and further facilitate transmission of viruses. In addition, the free vaccination for all people has been conducted in Macau to prevent the influenza. The Health Bureau ordered a total of 190,000 doses of the 2019–2020 quadrivalent influenza vaccine which will provide to people for free. Thus, these unique features should lead to unique research attention to the epidemiological characteristics of influenza in Macau, which should bring great value for preventing influenza in tourist cities in the world. So far, there has been no study published on the epidemiology of influenza in Macau. Therefore, we conducted this study to explore the epidemiological characteristics of influenza in Macau.

We collected and analysed influenza data from outpatients with influenza-like illness (ILI) at Kiang Wu Hospital in Macau from 2010 to 2018. The annual distribution of influenza A and B were determined. Three special influenza epidemics were found. Influenza data among different ages, genders, areas and seasons were calculated and compared. Our study can provide understanding on the epidemiological characteristics of influenza in Macau. The findings could help the prevention of influenza in Macau and over the world.

Materials and Methods

Data Collection

Our study was conducted at Kiang Wu Hospital in Macau from January 2010 to December 2018. Patients were enrolled when they presented with symptoms of influenza-like illness. The criteria for influenza-like illness was a sudden onset of spontaneous fever accompanied by at least one respiratory symptom (cough, sore throat, or running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness) (Butler *et al.* 2020). We enrolled a total of 104,874 outpatients with influenza-like symptoms and collected their throat and/or nasal swabs to test the influenza type using the BD Veritor System for rapid detection of Flu A + B reagent. Results were presented on a standard reporting format. Patients' demographic information, including age, gender and place of residence were recorded.

Data Analysis

We calculated and compared every year and month positive rate of influenza A and B to reflect annual and monthly distribution. In addition, influenza data were categorized based on the patients' demographic information: age, gender, area and season. The effect of patient age was evaluated by considering the following age groups; 0–4, 5–10, 11–17, 18–39, 40–64 and over 64 years old (Brownstein *et al.* 2005). The area was classified by locals and tourists. The influenza A in July 2017 and influenza B in January–February 2012 and January–February 2018 were analyzed separately due to their specificity.

The influenza data was summarized by ratios and percentages. Chi-square test was used to assess the significance of the association between variables and influenza infection. Binary multivariable logistics regression (Wagner *et al.* 2017) was conducted to assess potential risk factors associated with infection of influenza A and B. Binary multivariable logistics regression included age, gender, area and season. Odds ratio (OR) was obtained from the logistic regression model and indicated the strength of association between risk factors and influenza. In our study, all analyses were conducted in R language (R-3.4.3). Significance was assessed at an α level of 0.05, and precision was evaluated with 95% confidence intervals (95% CI).

Results

Influenza Changes Over the Years and Months

From January 2010 to December 2018, 104,874 samples with ILI were collected at Kiang Wu Hospital, Macau. The samples contained 17,973 cases (17.14%) of influenza A and 7274 cases (6.94%) of influenza B. The information of each year samples was shown in Table 1.

The number of ILI samples were increasingly collected and the number of samples in 2018 was twice as many as in 2010 (9368 cases in 2010 and 20,261 cases in 2018). The positive rate of influenza was relatively stable in these

Table 1 Annual distribution of influenza cases at Kiang Wu Hospital in Macau, 2010–2018.

Year	Samples	Influenza (%)	Influenza A (%)	Influenza B (%)
2010	9368	1695 (18.09)	1203 (12.84)	492 (5.25)
2011	6997	1608 (22.98)	1489 (21.28)	119 (1.70)
2012	13,054	3674 (28.14)	2209 (16.92)	1465 (11.22)
2013	6543	1178 (18.00)	1096 (16.75)	82 (1.25)
2014	8833	2504 (28.35)	2037 (23.06)	467 (5.29)
2015	11,427	2826 (24.73)	2124 (18.59)	702 (6.14)
2016	12,563	2880 (22.92)	1740 (13.85)	1140 (9.07)
2017	15,828	4122 (26.04)	3693 (23.33)	429 (2.71)
2018	20,261	4760 (23.49)	2382 (11.76)	2378 (11.74)
Total	104,874	25,247 (24.07)	17,973 (17.14)	7274 (6.94)

years, ranging from 18% to 28%. The positive rate of influenza A ranged from 10% to 25% and the positive rate of influenza B ranged from 1% to 10%. In most years, the positive rate of influenza A was greater than influenza B. However, influenza B showed unique activity in 2012 and 2018. The ILI sample number and positive rate in 2012 and 2018 (11.22% in 2012 and 11.74% in 2018) were higher than that in remaining years.

The total number and the mean month positive rate of influenza A and B were showed in Fig. 1 to explore the seasonality of the influenza epidemic. The positive rates in 2012, 2017 and 2018 were different from the remaining years. Note, for convenience of description, we denote the years except these three years as the normal years. First, the positive rate of influenza A in July 2017 was higher (> 40%) than in the normal years. In addition, the peaks of the influenza B in 2012 and 2018 appeared in January and February with the positive rate (close to 30%) was higher than that in the normal years. In the normal years, the incidence of influenza A occurred year-round and did not show seasonality (Fig. 1A). The positive rates of influenza A in January and February were slightly higher than other months (Fig. 1B). Influenza B showed seasonality with the peak appeared in spring (March to May) (Fig. 1C). The positive rates of influenza B in other months were very low (Fig. 1D).

Epidemiology of Influenza in the Normal Years

The influenza data in the normal years, including 2010–2011 and 2013–2016, were analyzed. A total of 55,731 ILI samples were included, of which 9689 (17.39%) cases were influenza A and 3002 (5.39%) cases were influenza B. The influenza data were classified by age (0–4,

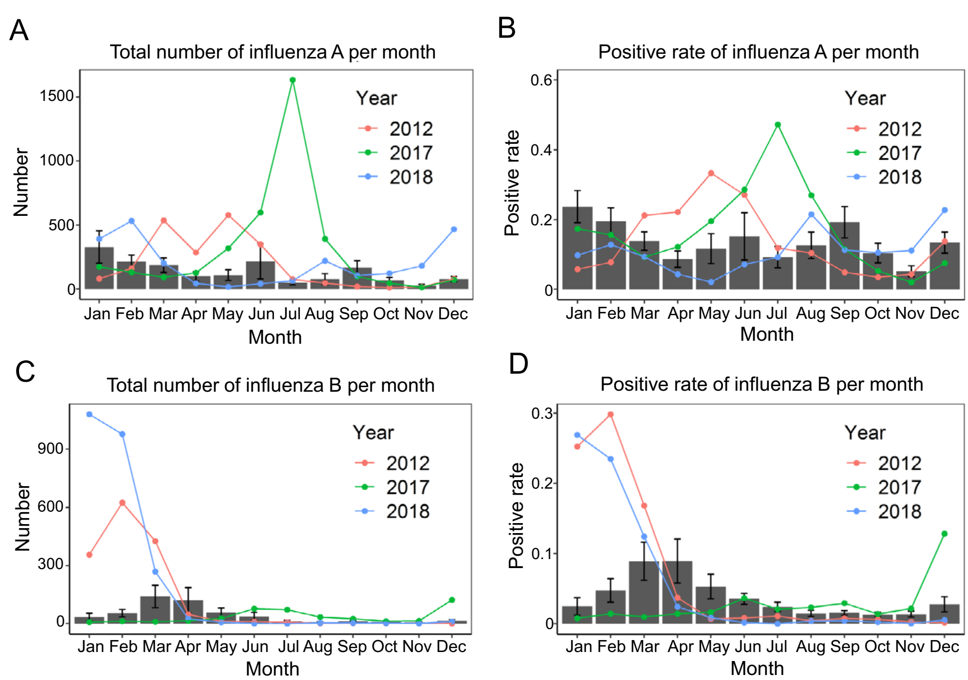

Fig. 1 Distribution of influenza A and influenza B. **A** Total number of influenza A per month. Positive rate of influenza A per month. **B** Positive rate of influenza A per month. **C** Total number of influenza B per month. **D** Positive rate of influenza B per month. The histograms represent the mean number or mean positive rate in the normal years (2010–2011 and 2013–2016). The error bars represent the standard error. The red, green and blue lines represent the trend of influenza A or influenza B in 2012, 2017 and 2018, respectively.

5–10, 11–17, 18–39, 40–64 and > 64 years), gender (female and male), area (local and tourist), and season (spring, summer, autumn and winter). Figure 2 showed the distribution of classified influenza data. Table 2 showed the results of univariate analysis, i.e. Chi-square test.

The number of ILI samples aged 0–4 years old was the highest among all age groups, accounting for 42.5% of the total. Children were thus the most prone to ILI symptoms and were willing to go to the hospital for diagnosis and treatment. The positive rate of influenza A and influenza B in 0–4 year-old group (influenza A: 12.8%; influenza B: 2.8%) and the > 64 year-old group (influenza A: 13.2%; influenza B: 2.3%) were low compare to other age groups (Fig. 2A). The positive rate of influenza A was highest in 18–39 year-old group (23.9%), while the positive rate of influenza B was highest in 5–10 year-old group (11.5%). The results of Chi-square test proved that the difference among different age groups was significant (influenza A: $P < 2 \times 10^{-16}$; influenza B: $P < 2 \times 10^{-16}$).

ILI samples were classified by gender (28,590 females and 27,141 males). We calculated and compared the positive rate of influenza A and influenza B in female and male. The positive rates of influenza A and B in females were slightly higher than those in males (influenza A: 17.59% for female and 17.17% for male; influenza B: 5.45% for female and 5.32% for male) (Fig. 2B). The Chi-square test indicate no significant difference between females and males (influenza A: $P = 0.1943$; influenza B: $P = 0.488$).

We divided ILI samples into local and tourists. The positive rates of influenza A and B among tourists were higher than that among locals (influenza A: 17.10% for local vs 21.90% for tourist; influenza B: 5.33% for local vs 6.23% for tourist) (Fig. 2C). The Chi-square test proved that the difference was significant between local and tourist (influenza A: $P < 2 \times 10^{-12}$; influenza B: $P = 0.0306$).

The epidemic of influenza also varied season by season. ILI samples were mostly collected during spring and winter. The positive rate of influenza A was the highest in winter (22.6%) and the lowest in spring (12.9%) (Fig. 2D). But the positive rate of influenza B was the highest in spring (10.4%). The results of Chi-square test proved that the difference among different season is significant (influenza A: $P < 2 \times 10^{-16}$; influenza B: $P < 2 \times 10^{-16}$).

Binary multivariable logistic regression was used to explore risk factors associated with influenza A and B. The variables include age, gender, area and season. The forest plot of logistic regression was showed in Fig. 3A, 3B and the detailed values of logistic regression were shown in Supplementary Table S1. First, for different age groups, the odds of influenza A and B were lower in the 0–4 year-old group and > 64 year-old group than other age group. The odds of influenza A in the 11–17 years-old group were twice as that in the 0–4 year-old group (OR = 2.21, $P < 2 \times 10^{-16}$). The 11–17 year old group showed the highest odds of influenza A. The odds of influenza B in the 5–10 year-old group were 4 times higher than the odds in 0–4 year-old group (OR = 4.38, $P < 2 \times 10^{-16}$). The 5–10 year-old group had the highest odds of influenza B. Secondly, consistent with the results of Chi-square test, the results of binary multivariable logistic regression showed that no significant difference in infections of influenza A

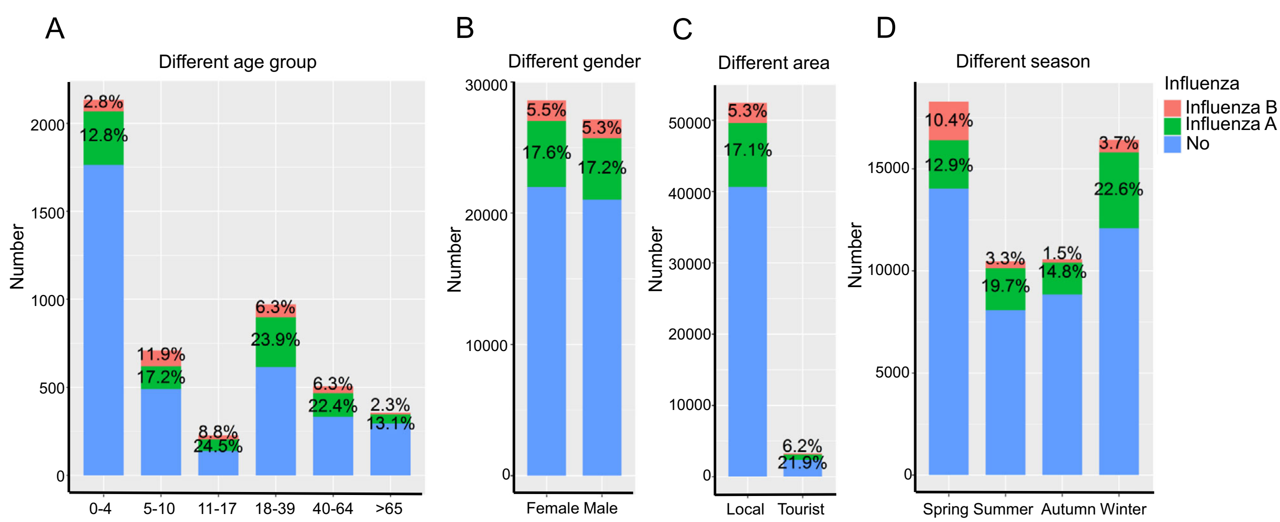

Fig. 2 Distribution of influenza A and influenza B among different age, gender, area and season in the normal years. **A** The number and positive rate of influenza A and B in different age groups. **B** The number and positive rate of influenza A and B in different genders. **C** The number and positive rate of influenza A and B in different areas. **D** The number and positive rate of influenza A and B in different seasons.

Table 2 Chi-square test results of influenza A and B by age, gender, area, and season in normal years.

Variable	Samples	Influenza A		Influenza B	
		Number (%)	Chi-square	Number (%)	Chi-square
Age					
0–4	23,710	3039 (12.82)	$\chi^2 = 949.75$	658 (2.78)	$\chi^2 = 1110.6$
5–10	7492	1288 (17.19)	$P < 2 \times 10^{-16}$	894 (11.93)	$P < 2 \times 10^{-16}$
11–17	2696	660 (24.48)		236 (8.75)	
18–39	11,798	2824 (23.94)		741 (6.28)	
40–64	6036	1354 (22.43)		381 (6.31)	
> 64	3999	524 (13.10)		92 (2.30)	
Gender					
Female	28,590	5029 (17.59)	$\chi^2 = 1.68$	1559 (5.45)	$\chi^2 = 0.48$
Male	27,141	4660 (17.17)	$P = 0.1943$	1443 (5.32)	$P = 0.488$
Area					
Local	52,439	8968 (17.10)	$\chi^2 = 49.35$	2797 (5.33)	$\chi^2 = 4.68$
Tourist	3292	721 (21.90)	$P < 2 \times 10^{-12}$	205 (6.23)	$P = 0.0306$
Season					
Spring	18,288	2357 (12.89)	$\chi^2 = 653.94$	1901 (10.39)	$\chi^2 = 1406.5$
Summer	10,468	2059 (19.67)	$P < 2 \times 10^{-16}$	341 (3.26)	$P < 2 \times 10^{-16}$
Autumn	10,568	1566 (14.82)		153 (1.45)	
Winter	16,407	3707 (22.59)		607 (3.70)	

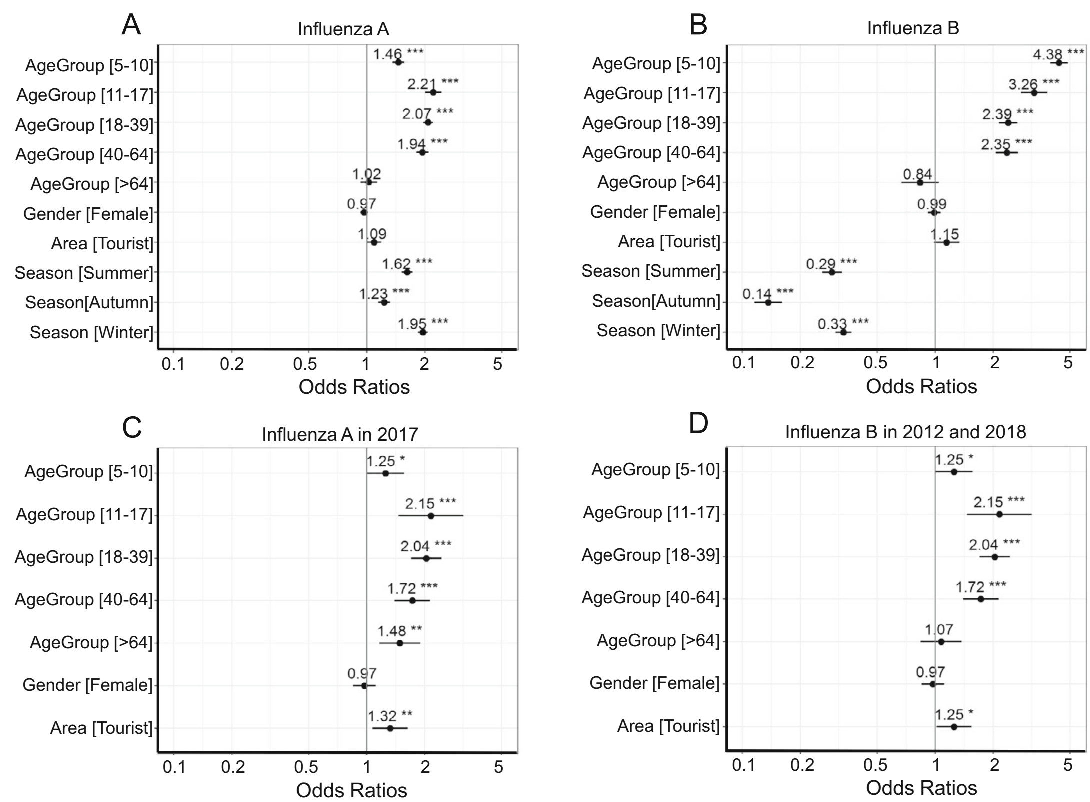

Fig. 3 Forest plot of binary multivariable logistic regression. **A** Binary multivariable logistic regression of influenza A in normal years. **B** Binary multivariable logistic regression of influenza B in normal years. **C** Binary multivariable logistic regression of influenza A in July 2017. **D** Binary multivariable logistic regression of influenza B in January–February 2012 and January–February 2018. The asterisk represents the significance level (*** < 0.001, ** < 0.01, * < 0.05).

and B between female and male. Thirdly, although the odds of influenza A and B in tourist was slightly higher than that in locals (influenza A: OR = 1.09, $P = 0.0557$; influenza B: OR = 1.15, $P = 0.0771$), the difference was not significant. The result is not the same as the result of the Chi-square test. The reason for this phenomenon is that the covariate affects the result of multiple logistic regression (Wang *et al.* 2017). Area was not a risk factor for infection of influenza A and B in the normal years. Finally, the odds of influenza A were the lowest in spring, while the odds of influenza B were the highest in spring.

Influenza A Epidemic in 2017

Because the epidemic of influenza A in July 2017 is different from the normal years, we extracted influenza A data in July 2017 and compared it with the data in July of normal years. The distribution of influenza A and the comparison between 2017 and normal years were showed in Table 3. A total of 3461 ILI samples were collected in July 2017, which exceeded the total samples of the normal years (2577 samples in six years). Also, the positive rate of influenza A in July 2017 was 47.2%, which was significantly higher than that (11.6%) in July of normal years ($P < 2 \times 10^{-16}$). The forest plot of logistic regression was showed in Fig. 3C and the detailed values of logistic regression were shown in Supplementary Table S2.

The Chi-square test and logistic regression show significant differences among different age groups. The odds of influenza A in the 11–17 year-old group (OR = 2.15, *P*-value = 0.0001) and 18–39 year-old group (OR = 2.04, *P* value = 1.29×10^{-14}) were twice as the odds of influenza A in 0–4 year-old group.

Consistent with the results in the normal years, the results of Chi-square test and logistic regression indicated there is no significant difference between male and female ($P = 0.5771$). However, the differences in influenza A infection between locals and tourists is significant. The odds of influenza A in tourists (OR = 1.32, *P* value = 0.0091) were significantly higher than local.

Influenza B Epidemic in 2012 and 2018

Because the epidemic of influenza B in January–February 2012 and January–February 2018 is different from the normal years, we extracted influenza B data in this period and compared it with the influenza B in January–February of normal years. The distribution of influenza B and the comparison between 2012, 2018 and normal years were showed in Table 4. A total of 11,677 ILI samples were collected in January–February 2012 and January–February 2018, which was close to the total samples of the normal years (13,206 samples in six years). Also, the positive rate of influenza B in January–February 2012 and January–February 2018 was 25.9%, which was significantly higher than that (3.9%) in January–February of normal years ($P < 2 \times 10^{-16}$). The forest plot of logistic regression was showed in Fig. 3D and the detailed values of logistic regression were shown in Supplementary Table S2.

Among different age groups, the odds of influenza B were the highest in the 5–10 year-old group (OR = 3.51, $P < 2 \times 10^{-16}$) and 11–17 year-old group (OR = 3.66, $P < 2 \times 10^{-16}$), and lowest in 0–4 year-old group and > 64 year-old group (OR = 1.07, $P = 0.3131$).

Consistent with the results in the normal years, the Chi-square test and logistic regression result showed no significant differences in infections of influenza B between

Table 3 Distribution and comparison of influenza A in July 2017.

Variables	Influenza A in 2017			Influenza A in normal		*P* value
	Samples	N (%)	*P* value	Samples	N (%)	
Age						
0–4	1335	519 (38.9)	$\chi^2 = 80.43$	1109	83 (7.5)	$< 2 \times 10^{-16}$
5–10	419	188 (44.9)	$P = 7 \times 10^{-16}$	269	28 (10.4)	$< 2 \times 10^{-16}$
11–17	116	68 (58.6)		116	14 (12.1)	3×10^{-13}
18–39	789	449 (56.9)		549	99 (18.0)	$< 2 \times 10^{-16}$
40–64	478	253 (52.9)		288	45 (15.6)	$< 2 \times 10^{-16}$
> 64	324	157 (48.5)		246	30 (12.2)	$< 2 \times 10^{-16}$
Gender						
Male	1679	784 (46.7)	$\chi^2 = 0.31$	1289	152 (11.8)	$< 2 \times 10^{-16}$
Female	1782	850 (47.7)	$P = 0.5771$	1288	147 (11.4)	$< 2 \times 10^{-16}$
Area						
Local	3042	1401 (46.1)	$\chi^2 = 13.11$	2414	273 (11.3)	$< 2 \times 10^{-16}$
Tourist	419	233 (55.6)	$P < 0.0003$	163	26 (15.9)	$< 2 \times 10^{-16}$
Total	3461	1634 (47.2)		2577	299 (11.6)	$< 2 \times 10^{-16}$

Table 4 Distribution and comparison of influenza B in January–February 2012 and January–February 2018.

Variables	Influenza B in 2012 and 2018			Influenza B in normal		Chi-Squre
	Samples	N (%)	*P* value	Samples	N (%)	
Age						
0–4	4369	675 (15.4)	$\chi^2 = 566.35$	5338	125 (2.3)	$< 2 \times 10^{-16}$
5–10	2362	926 (39.2)	$P < 2 \times 10^{-16}$	1561	129 (8.3)	$< 2 \times 10^{-16}$
11–17	647	260 (40.2)		667	32 (4.8)	$< 2 \times 10^{-16}$
18–39	2435	714 (29.3)		3302	138 (4.2)	$< 2 \times 10^{-16}$
40–64	1275	349 (27.4)		1494	79 (5.3)	$< 2 \times 10^{-16}$
> 64	589	110 (18.7)		824	15 (1.8)	$< 2 \times 10^{-16}$
Gender						
Male	5498	1384 (25.2)	$\chi^2 = 3.11$	6321	235 (3.7)	$< 2 \times 10^{-16}$
Female	6188	1650 (26.7)	$P = 0.0779$	6885	283 (4.1)	$< 2 \times 10^{-16}$
Area						
Local	10,486	2681 (25.6)	$\chi^2 = 9.01$	12,284	464 (3.8)	$< 2 \times 10^{-16}$
Tourist	1191	353 (29.6)	$P = 0.0027$	922	54 (5.9)	$< 2 \times 10^{-16}$
Total	11,677	3034 (25.9)		13,206	518 (3.9)	$< 2 \times 10^{-16}$

male (OR = 1.03, *P* value = 0.4670) and female. However, the differences in influenza B infection between locals and tourists were significant. The odds of influenza B in tourists (OR = 1.25, *P* value = 0.0474) were significantly higher than local.

Discussion

To investigate the epidemiological characteristics of influenza, we examined 104,874 samples with ILI in Macau from 2010 to 2018. This is the first time that the epidemiological characteristics of influenza are examined in Macau. Based on our analysis on these samples, we have the following findings. First, our results show that, among these ILI samples, the overall positive rate is 17.17% for influenza A and 6.97% for influenza B (Table 1). However, the influenza epidemics in three special years (i.e., 2012, 2017 and 2018) differed from the remaining years (i.e., normal years). The positive rate of influenza A in July 2017 (47.2%) was significantly higher than that in July of normal years (11.6%) and the positive rate of influenza B in January–February 2012 and January–February 2018 (25.9%) was significantly higher than that in January–February of normal years (3.9%). Second, in a normal year, influenza A did not show obvious seasonality, while influenza B was seasonal in Macau. Third, the odds of influenza A and B were lower in children (0–4 years old) and elderly (> 64 years old) than the four other age groups (5–10, 11–17, 18–39, 40–64 years old), but the difference of influenza A and B infection between male and female was not significant (Fig. 3). Finally, our analysis showed that in a normal year, there was no significant difference between locals and tourists in influenza A and B infection. However, in July 2017, the odds of influenza A in tourists were significantly higher than those in locals (OR = 1.32, *P* value = 0.0091) (Supplementary Table S2); in January–February 2012 and January–February 2018, the odds of influenza B in tourists were significantly higher than those in locals (OR = 1.25, *P* value = 0.0474) (Supplementary Table S2). We give discussions on these findings below.

Our results show that the overall positive rate is 17.17% for influenza A and 6.97% for influenza B. The positive rate of influenza in Macau is much lower than that in Myammar from 2010 to 2015 (influenza A: 55.1%; influenza B: 28.3%) (Htwe *et al.* 2019), and also lower than or close to the positive rate of influenza in Ethiopia from 2009 to 2015 (20.6%) (Woyessa *et al.* 2018) and in tropical Asia from 2007 to 2013 (South China: 17.3%; Thailand: 18%; Philippines: 17.2%; Singapore: 24.6%) (Durand *et al.* 2016). It indicates that the influenza in Macau is well controlled although Macau is a city with the highest population density and a large population mobility. Our results also show that the number and positive rate of influenza A were generally higher than those of influenza B. Influenza A viruses were predominant in most of the season; influenza B viruses predominated in spring (March to May) (Fig. 1). The trend and peak of influenza A and B in USA (Blanton *et al.* 2017; Garten *et al.* 2018; Xu *et al.* 2019) is similar to that in Macau.

Our analysis shows an age effect. That is, the odds of influenza A and B were lower in the children and elderly than the four other age groups in Macau. The similar age effect is also reported in Ethiopia (Woyessa *et al.* 2018). There may be the following three reasons about this age effect. First, as a common belief, influenza can cause more damage to the health of the children and elderly. Thus, these two age groups are more likely to get vaccination than the other four age groups, leading to a better prevention of influenza that resulted in a lower odd of influenza in the children and elderly. Second, children and elderly cannot express their symptoms very clear. Thus, some of them with mild influenza symptoms will also be considered as ILI samples. The inclusion of these samples increases the total number of samples, but the number of influenza cases remains unchanged, so the positive rate in children and elderly is low.

Our results show that Macau experienced a special epidemic of influenza A in the summer season of 2017 and two special epidemic of influenza B in January–February 2012 and January–February 2018. The number and positive rate of influenza A or influenza B were significantly higher in these special years than that in normal years either in tourists or in locals. The epidemic of influenza A similar to what it is in Taiwan and Hong Kong because the influenza season in Taiwan and Hong Kong in 2016 and 2017 also showed an unusual summer peak mainly due to the spread of influenza A (H3N2) virus (Tsou *et al.* 2017; Chiu SS *et al.* 2018). The epidemic of influenza B in January–February 2012 and January–February 2018 in Macau coincided with the influenza B epidemic in mainland China. During the winter season of 2012–2013 and 2017–2018, China experienced a nationwide influenza epidemic mainly caused by influenza B virus which belonged to the Yamagata lineage (Radovanov *et al.* 2015; Saha *et al.* 2016; Li *et al.* 2019; Zhu *et al.* 2019). This phenomenon shows that three special influenza epidemics in Macau is closely related to its neighboring areas. The mobility of tourists has caused the virus to spread to locals, thus increasing the numbers and positive rates of influenza in locals.

One important finding in our study is that, there is no significant difference between locals and tourists in influenza A and B infection in a normal year (Fig. 3A, 3B) whereas the odds of influenza A in tourists were significantly higher than those in locals in July 2017 (Fig. 3C) and the odds of influenza B in tourists were significantly higher than those in locals in January–February 2012 and January–February 2018 (Fig. 3D). This finding further revealed that the epidemic of influenza in Macau is affected by the mobility of tourists. Moreover, Macau government provides free seasonal influenza vaccination to all permanent residents. The free vaccination starts around October each year and is provided to high-risk groups first. Then, around December, the free vaccination is extended to all residents. A survey revealed that the estimated proportion of the total population covered by the number of vaccines purchased in Macau is 19.8% in 2011, which is higher than its neighboring areas (6.8% in Hong Kong) (Dwyer *et al.* 2013). With the further implementation of government propaganda work, the dose of vaccine purchased by the government is increasing (110,000 doses in 2011 vs 190,000 doses in 2019), and the number of residents receiving influenza vaccine is increasing (about 85,000 in 2011 vs about 160,000 in 2019). The vaccination rate is over 80% for kindergarten children, over 70% for primary school students and almost 40% for elderly. Therefore, compared with tourists, the higher vaccination rate of locals can effectively reduce the incidence of influenza among locals. This may also support that vaccination is an important way to prevent influenza.

The influenza data in Macau could contribute to study on the circulation pattern of influenza and help the prevention of influenza not only in Macau but also in Hong Kong, Taiwan and other regions in the world. Our epidemiological study on influenza A and B could be helpful to prevent influenza in Macau and provide guidance on vaccine strain selection and adjustment of time for vaccination. Vaccination is the most effective approach to reduce the prevalence of influenza (Rolfes *et al.* 2019; Sah *et al.* 2019). Although Macau is a city with a high density and a large mobility of population, the influenza in Macau is well controlled, which is attributed to the employment of free vaccination for all people in Macau. Therefore, we hope that free vaccination could be employed in more regions in the future.

In sum, we analyzed the epidemiological characteristics of influenza A and B in Macau and found that influenza in Macau has been well controlled, which may benefit from the implementation of free vaccination for all people in Macau. Further studies are needed to explore the contribution of vaccine teammates to control influenza in Macau in combination with detailed influenza vaccination data in Macau.

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Author Contributions XDZ and JLN conceived the study with input from all co-authors. HMN, SMK, MIW, CHW and JLN collected the data. TZ, GLW, GYM, ZL, CC and DDW did the data analyses and HMN, TZ, XDZ and JLN performed the interpretation of the data. HMN and TZ wrote the first draft of the manuscript, and XDZ revised and approved the final manuscript. All authors contributed to the final version and agreed to the submission.

Compliance with Ethical Standards

Conflict of interest The authors have declared that no competing interest exists.

Animal and Human Rights Statement This study was conducted with the approval of the Animal Ethics Committee of Kiang Wu Hospital in Macau.

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