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Brief Original Article

Influenza virus subtype/lineage-specific seasonal patterns and age-related infection risk, in Eastern China

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Abstract

Introduction: Differences in seasonal pattern and age-related infection risk have been reported between Influenza type A and B, but have not been elaborated at subtype/lineage level.

Methodology: All laboratory-confirmed influenza cases reported in the influenza surveillance system of Jiangsu Province, China from January 2011 to August 2019 were analyzed. Influenza seasonality was characterized using the Seasonal Decomposition method. Binary and multinomial logistic regressions were employed to calculate the odds ratios of influenza subtypes/lineages in relation to age.

Results: A total of 28,772 confirmed influenza cases were included. Among them, a majority (64.1%) were influenza A infections. One annual peak was observed for A (H1N1) pdm and B-Yamagata in winter months, and for B-Victoria in spring months, while biannual peaks were observed for A (H3N2) in winter and summer months. Using all ages as the reference, children younger than 5 years and adults of 25-59 years were more likely to infect with A (H1N1) pdm. Older children aged 5-14 years had significantly higher odds of infection with influenza B of both lineages, while individuals aged 15-24 years had higher odds for A (H3N2) and B-Victoria. The elderly (60 years or older) were prone to be infected with A (H3N2) and B-Yamagata. For a specific age group, their likelihood of getting infected with an influenza subtype or lineage was related to the co-circulating influenza subtype or lineage.

Conclusions: Influenza viruses have divergent seasonal peak times and age-related infection risk at subtype/lineage level.

Key words: Influenza; subtype; lineage; Age; risk; seasonality.

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Introduction

The response of influenza virus activity to meteorological factors is viral type-dependent [1,2], resulting in a different seasonal pattern between influenza type A and B [3,4]. However, few studies investigated this issue at the influenza subtype/lineage level, which limited our early preparation and precise response to subtype/lineage-specific epidemics. Co-circulation of two or more influenza subtypes and lineages is common. It is important to know the likelihood of being infected with an influenza subtype/lineage in relation to its co-circulating influenza subtypes/lineages, and if the likelihood is age-dependent or not. This will allow us to recognize the at-risk subpopulations when facing an epidemic caused by a specific combination of several influenza subtypes/lineages. Differential age-specific distribution of influenza virus types and subtypes have been indicated [5–7], but that of influenza virus lineages has not been clearly demonstrated. In this study, we aim to depict the seasonal patterns and age-specific cross-referencing infection risk at influenza virus subtype/lineage level.

Methodology

Subjects

Jiangsu province, situated in the Yangzi River Delta Region of eastern China, is a transitional district with warm temperate to subtropical zones. As a part of the national influenza surveillance network, influenza-like-illness (ILI) outpatients (defined as body temperature ≥ 38 °C with a cough and/or a sore throat) and their respiratory specimens are reported and collected in a weekly manner by 29 sentinel hospitals in Jiangsu, via China Influenza Surveillance Information System (CISIS). No less than 20 specimens are required to be collected from each sentinel site for each week. All the samples are sent to local network influenza laboratories in 48 hours after collection and are typed/subtyped by real-time fluorescent quantitative PCR assay in 72

hours for influenza A (H1N1pdm and H3N2) and B (Victoria and Yamagata). All laboratory-confirmed influenza cases reported in this system from January 2011 to August 2019 were included in this study.

Statistical analysis

Frequencies of detected influenza subtypes and lineages were aggregated monthly for seasonal pattern analyses. Seasonal factors were computed as indicators of seasonality, using Seasonal Decomposition method. A positive value of seasonal factor represents an additive seasonal effect on incidence, while a negative value represents a reductive effect. We divided Jiangsu province into three regions, i.e., north, middle, and south, based on geographical location and economic development level. Pearson chi-squared test was used for comparing proportions. Binary logistic regression was used to calculate the infection odds ratios for A (H1N1) pdm, A (H3N2), B-Victoria and B-Yamagata, respectively. Multinomial logistic regression was employed to quantify the age-specific infection likelihood of co-circulating influenza subtypes/lineages, generating a cross-referencing odds ratios table. Study variables with statistical significance in univariate analyses were then included in multivariate analysis. Statistical analyses were performed by IBM SPSS Statistics 25 and statistical significance was set at $p \leq 0.05$. Cases with missing data in variables being analyzed were excluded.

Results

A total of 28,772 confirmed influenza cases were included in this study, during an over eight years surveillance period. Influenza A infections accounted for a major proportion of 64.1%. Among them, the frequency of A (H3N2) infections was about 1.5 times as that of A (H1N1) pdm infections. Most of the influenza B viruses were further determined by lineages (88%), among whom the proportion of B-Victoria was slightly higher than that of B-Yamagata (52.1% vs. 47.9%).

The frequency of detected influenza cases varied across months and years. The monthly frequency ranged from 4 to 1,259 during the study period. Winter peaks were observed yearly, while summer peaks presented in a half (2012, 2014, 2015, and 2017) of the years with year-round data (2011-2018) (Figure 1).

Seasonal patterns differed by influenza subtypes/lineages. A single annual peak was observed for A (H1N1) pdm and B-Yamagata in winter months, and for B-Victoria in spring months, while biannual peaks were observed for A (H3N2) only (Figure 2). According to the seasonal factors, the seasonal additive effect on the incidence of A (H3N2) and B-Yamagata occurred as early as December and lasted till next January and March, respectively. That of A (H1N1) pdm took place from January to March. Then, a lagged additive effect on B-Victoria incidence would follow (from March to May). In addition, another additive effect on the incidence of A (H3N2) was presented in the summer months (from July to September). All the influenza summer peaks we observed during the study period were caused by A (H3N2) (Figure 2).

Most of the influenza cases included in this study were local residents of Jiangsu Province (28,161, 97.9%). Among cases from the north, middle, and south region of Jiangsu, the proportions of detected influenza subtypes and lineages differed significantly ($p < 0.0001$), although A (H3N2) consistently accounted for the most in each region. Compared with other regions, A (H3N2) and B-Victoria accounted for a higher proportion in the middle region, A (H1N1) pdm's proportion was higher in the north region and B-Yamagata's proportion was higher in the south region (Table 1).

Significant differences were not observed in the distributions of influenza subtypes and lineages between genders ($p = 0.238$) but were found among age

Figure 1. Monthly frequencies of detected influenza cases by (sub)types from January 2011 to August 2019.

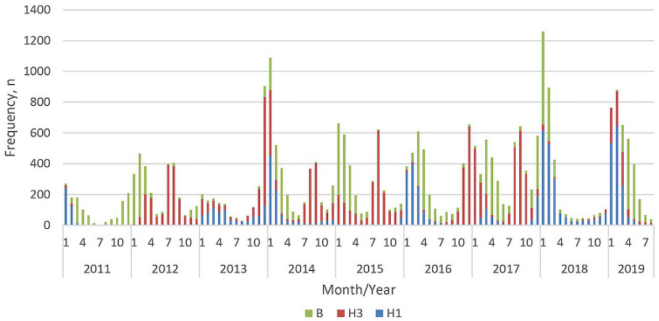

Figure 2. Influenza subtype/lineage-specific seasonal factors by months.

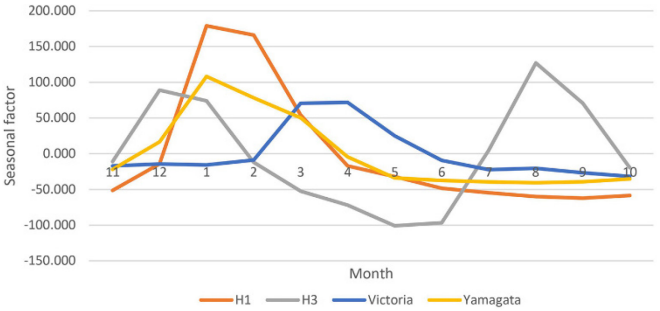

Table 1. Distributions of influenza subtype/lineages among selected variables (n = 27,530).

Studied variables	A(H1N1) pdm	A(H3N2)	B-Victoria	B-Yamagata	*p* value
Age, years, n (%)					< 0.0001
< 5	2679 (30.4)	3600 (40.8)	1358 (15.4)	1178 (13.4)	
5-14	1815 (22.9)	2714 (34.3)	1882 (23.8)	1504 (19.0)	
15-24	544 (23.4)	1074 (46.3)	417 (18.0)	287 (12.4)	
25-59	1880 (27.5)	2942 (43.0)	959 (14.0)	1061 (15.5)	
≥ 60	359 (21.9)	837 (51.2)	118 (7.2)	322 (19.7)	
Gender					0.238
Male	3870 (26.7)	5892 (40.7)	2430 (16.8)	2280 (15.8)	
Female	3407 (26.1)	5275 (40.4)	2304 (17.6)	2072 (15.9)	
Region of Jiangsu[a]					< 0.0001
North	2483 (31.2)	2892 (36.3)	1339 (16.8)	1247 (15.7)	
Middle	2438 (23.6)	4515 (43.7)	1882 (18.2)	1506 (14.6)	
South	2170 (25.1)	3536 (41.0)	1407 (16.3)	1519 (17.6)	

[a] Only local residents of Jiangsu were analyzed (n = 26,934).

groups ($p < 0.0001$). Over half (51.2%) of the elderly influenza cases (60 years or older) were infected with A (H3N2), but the proportion was much lower in children cases aged 5-14 years (34.3%). The proportion accounted by A (H1N1) pdm in children cases younger than 5 years was the highest (30.4%), and that of B-Victoria in children cases aged 5-14 years was the highest (23.8%), compared with that in other age-groups. To be noted, the proportion of B-Yamagata in cases of 60 years or older was the highest (19.7%), closely followed by that in children cases aged 5-14 years (19.0%), compared with that in other age groups (Table 1).

After adjusting by cases' residential regions, binary logistic regression analyses showed that, compared with all ages, children younger than 5 years (OR = 1.235, 95% CI, 1.172 - 1.301) and adults of 25-59 years (OR = 1.161, 95% CI, 1.099 - 1.227) were more likely to infect with A (H1N1) pdm. Older children aged 5-14 years had significantly increased odds for infection with influenza B of both lineages (OR = 1.786, 95CI, 1.676 - 1.903 for B-Victoria; OR = 1.279, 95% CI, 1.203 - 1.359 for B-Yamagata). Individuals aged 15-24 years had a higher likelihood of being infected with A (H3N2) (OR = 1.138, 95% CI, 1.060 - 1.221) and B-Victoria (OR = 1.270, 95% CI, 1.155 - 1.398), while the elderly (60 years or older) were prone to be infected with A (H3N2) (OR = 1.371, 95% CI, 1.264 - 1.487) and B-Yamagata (OR = 1.295, 95% CI, 1.168 - 1.436) (Table 2).

Influenza subtypes/lineages circulate alternately, and an epidemic is usually dominated by two or more subtypes/lineages. To demonstrate the likelihood of being infected with an influenza subtype/lineage with its co-circulating influenza subtypes/lineages, we further employed a multinomial logistic regression to illustrate the cross-referencing infection odds ratios (Table 3). The cross-reference results were consistent with those of binary logistic regression analyses, and provide more practical information. Take the elderly (60 years or older) for instance, they were prone to infection with both A (H3N2) and B-Yamagata as suggested by binary logistic regressions, however, when A (H3N2) and B-Yamagata co-circulated, they were more likely to get infected with B-Yamagata than with A (H3N2) (OR: 1.158, 95% CI: 0.999 - 1.343), compared with children younger than 5 years old. In another scenario, although the elderly were less likely to get infected with A (H1N1) pdm and B-Victoria when these two strains co-circulated, they were more vulnerable to infecting with A (H1N1) pdm over infecting with B-Victoria (OR: 1.670, 95% CI: 1.338 - 2.083), compared with children younger than 5 years old (Table 3).

Discussion

During our study period, influenza A infections accounted for a major proportion of 64.1%, which is in line with that at a national (China), Asia-Pacific regional, and global scale [3,8]. Previous studies

Table 2. Age-specific infection odds ratios (95% CI) for influenza subtype/lineages, using binary logistic regressions (n = 26,934).

Age, years	A (H1N1) pdm	A (H3N2)	B-Victoria	B-Yamagata
< 5	1.235 (1.172 - 1.301)	0.933 (0.890 - 0.978)	1.065 (0.995 - 1.140)	0.849 (0.795 - 0.906)
5-14	0.880 (0.833 - 0.930)	0.690 (0.658 - 0.724)	1.786 (1.676 - 1.903)	1.279 (1.203 - 1.359)
15-24	0.919 (0.846 - 0.998)	1.138 (1.060 - 1.221)	1.270 (1.155 - 1.398)	0.744 (0.670 - 0.825)
25-59	1.161 (1.099 - 1.227)	0.995 (0.948 - 1.044)	0.933 (0.868 - 1.003)	0.957 (0.896 - 1.022)
≥ 60	0.862 (0.782 - 0.951)	1.371 (1.264 - 1.487)	0.444 (0.381 -0.517)	1.295 (1.168 - 1.436)

* Adjusted by cases' residence regions; To obtain the odds ratios for each age group, we use the overall effect of the age variable as the reference.

indicated that influenza type B peaked later than type A in temperate zones [3]. Our results found that influenza B-Victoria peaked later than influenza A, while B-Yamagata could peak with influenza A, in particular with A (H1N1) pdm. This underscores the necessity to perform a time series study and prediction study of the influenza virus at subtype/lineage-level. As influenza seasonality is a climate-dependent [2]. The differential seasonal patterns by influenza subtype/lineages need to be investigated and compared across climate zones.

Jiangsu province locates at 30° 45'~35° 08' N, which is a transitional district from a warm temperate to a subtropical zone. A systematic analysis of global patterns in the monthly activity of the influenza virus indicated that summer peaks were observed within the latitude range [9]. As described in a previous National study of China [10], Jiangsu Province was characterized as a province of semi-annual peaks of influenza A between January–Februrary, and June–August, and an annual peak of influenza B, which is similar to our results. Our study presents further information at the subtype and lineage level. We found that the A (H3N2) subtype could peak as early as December, B-Victoria mainly peaked during the spring months, and the summer peak of influenza was always due to the A (H3N2) subtype.

Influenza B can dominate influenza seasons and cause severe disease, particularly in children and adolescents [11,12]. Our results showed that the odds of catching B-Victoria were significantly higher in children and adolescents (5-24 years), while the odds of infecting with B-Yamagata were significantly higher in children aged 5-14 years and the elderly (60 years or older). Our results coincide with previous observations [13,14] and present the quantitative infection odds further. As the elderly are more likely to have severe influenza B-related pneumonia, our results also highlight the importance of implementing a quadrivalent influenza vaccine in this population.

As co-circulation of influenza subtypes/lineages is common, the cross-referencing age-specific infection odds, presented by this study for the first time, are of great public health significance. For instance, when A (H1N1) pdm co-circulates with A (H3N2), the elderly (60 years and older) are more likely to be infected with A (H3N2), while when A (H1N1) pdm co-circulates with B-Victoria, the elderly are inclined to catching A (H1N1) pdm, compared with children younger than 5 years. Our results could greatly help public health experts and healthcare workers identify the at-risk subpopulations when facing an epidemic caused by a specific combination of influenza subtypes/lineages.

Conclusions

Influenza viruses have divergent seasonal peak times and age-related infection risk at the subtype/lineage level. Our results could inform the better implementation of precise prevention and control measures against influenza.

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Table 3. Cross-referencing age-specific infection odds of influenza subtype/lineages (n = 26,934).

Age	Ref.	A (H1N1) pdm	A (H3N2)	B-Victoria	B-Yamagata
60-	A (H1N1) pdm	NA	1.603 (1.398 -1.837)	0.599 (0.480 - 0.747)	1.856 (1.567 - 2.198)
	A (H3N2)	0.624 (0.544 - 0.715)	NA	0.374 (0.304 - 0.459)	1.158 (0.999 - 1.343)
	B-Victoria	1.670 (1.338 - 2.083)	2.676 (2.179 - 3.286)	NA	3.099 (2.466 - 3.894)
	B-Yamagata	0.455 (0.539 - 0.638)	0.745 (0.864 - 1.001)	0.257 (0.323 - 0.405)	NA
25-59	A (H1N1) pdm	NA	1.082 (0 .998 - 1.173)	0.932 (0.837 - 1.037)	1.156 (1.038 - 1.287)
	A (H3N2)	0.924 (0.852 - 1.002)	NA	0.861 (0.779 - 0.953)	1.069 (0.966 - 1.183)
	B-Victoria	1.073 (0.964 - 1.194)	1.161 (1.050 - 1.284)	NA	1.241 (1.097 - 1.403)
	B-Yamagata	0.865 (0.777 - 0.963)	0.936 (0.845 - 1.035)	0.806 (0.713 - 0.911)	NA
15-24	A (H1N1) pdm	NA	1.389 (1.235 - 1.562)	1.438 (1.242 - 1.665)	1.108 (0.942 - 1.302)
	A (H3N2)	0.720 (0.640 - 0.810)	NA	1.036 (0.908 - 1.182)	0.798 (0.687 - 0.926)
	B-Victoria	0.695 (0.600 - 0.805)	0.966 (0.846 - 1.102)	NA	0.770 (0.648 - 0.915)
	B-Yamagata	0.903 (0.768 - 1.061)	1.254 (1.080 - 1.455)	1.298 (1.093 - 1.543)	NA
5-14	A (H1N1) pdm	NA	1.064 (0.983 - 1.152)	1.945 (1.770 - 2.136)	1.808 (1.638 - 1.996)
	A (H3N2)	0.940 (0.868 - 1.018)	NA	1.828 (1.674 - 1.995)	1.699 (1.548 - 1.865)
	B-Victoria	0.514 (0.468 - 0.565)	0.547 (0.501 - 0.597)	NA	0.930 (0.836 - 1.034)
	B-Yamagata	0.553 (0.501 - 0.611)	0.588 (0.536 - 0.646)	1.075 (0.968 - 1.196)	NA

* The reference age-group is individuals younger than 5 years; NA indicates not applicable; The ORs are adjusted by cases' residence regions.

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