WITHDRAWN: Epidemic patterns of the different influenza virus types and subtypes/lineages for 10 years in Chongqing, China

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The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.
Abstract

**Objectives** To optimize seasonal influenza control and prevention programs in regions with potentially complicated seasonal patterns.

**Methods** Descriptive epidemiology was used to analyze the etiology of influenza, and chi-square tests were used to compare the epidemic patterns among different influenza virus types and subtypes/lineages.

**Result** From January 2010 to December 2019, a total of 63,626 ILI cases were reported in Chongqing and 14,136 (22.22%) were laboratory-confirmed influenza cases. The positive rates of influenza A and influenza B, which were 13.32% and 8.86%, respectively. The positive rate of influenza A reached the highest in winter (23.33%), while the positive rate of influenza B reached the highest in spring (11.88%). Children aged 5-14 years old had the highest positive rates of influenza. The influenza virus types/subtypes positive was significantly different by seasons and age groups (p < 0.001), not by gender (p=0.436). The vaccine strains were matched to the circulating influenza virus strains in all other years except for 2018 (circulating strain was B/Yamagata).

**Conclusions** The study showed significant variations in epidemic patterns, including seasonal epidemic period and age distributions, among different influenza types, subtypes/lineages in Chongqing. Influenza vaccines matched well to the circulating influenza virus strain. In order to prevent and mitigate the influenza outbreak in this area, high risk population, especially children aged 5-14 years, should be encouraged to get vaccinated against influenza before the epidemic season.

Introduction

Influenza is an acute respiratory infectious disease caused by influenza virus. According to viral nuclear protein and matrix protein, it is divided into A, B, C and D, of which influenza A virus is the most common type [1, 2]. Each year, about 10% of adults and 20% of children worldwide are infected with influenza, resulting in an estimated one billion cases, 3–5 million hospitalizations, and 290,000–650,000 respiratory deaths globally [3–5]. Influenza causes an average of 88,000 additional respiratory deaths per year in China, with a vast area, complex climatic conditions, and a large population, yet the seasonality of influenza activity varies from region to region [6]. Previous studies have shown that the seasonality of influenza in subtropical zones is more variable.

Chongqing, located in southwest China, has a typical subtropical humid monsoon climate and is the largest municipality directly in China with over 30 million registered inhabitants [5]. It seems to have a more complex and irregular circulation pattern than other cities. However, studies comparing the epidemiology of influenza A and B infections are limited. This study aimed to compare the epidemic patterns of influenza A and B in Chongqing and to analyze the 2010–2019 epidemiological strains and vaccine matches to provide scientific evidence for optimizing influenza control and prevention.

**Materials and Methods**

**Influenza Surveillance**

Influenza-like illness (ILI) and influenza positive rates were obtained from sentinel influenza surveillance network in Chongqing, which had been stated in a previous study [7]. The ILI defined as having a fever (≥ 38.0°C) and either cough or sore throat, was diagnosed by the outpatient and emergency departments [8]. In each sentinel hospital, an average of 20 respiratory specimens (throat swab, nasal swab, or nasopharyngeal swab) were collected from ILI cases per week. Samples are stored at 2°C to 8°C and sent to the laboratory for reverse transcription-polymerase chain reaction (RT-PCR) to determine the types and subtypes/lineages of influenza virus according to the standard protocol. The positive rate was defined as the percentage of respiratory specimens tested positive for influenza viruses. In this study, we analyzed influenza surveillance data including gender, age, date of onset and laboratory testing results from January 2010 to December 2019.

**Statistical Analysis**

R software (version4.2.3) was used for data management and statistical analysis. Histogram and line charts were used to show the time distribution of influenza cases. Chi-square tests were used to compare the differences in categorical variables. A two tailed p value < 0.05 was considered statistically significant.

**Result**

**Overall characteristics of influenza cases**

From 2010–2019, 63,626 ILI cases were enrolled for specimen collection in sentinel hospitals. Among them, 34,878 (54.82%) were males and 28,748 (45.18%) were females. A total of 14,136 ILI cases were diagnosed with laboratory-confirmed influenza. The overall positive rate of influenza virus was 22.22%. Regarding seasonality of influenza positive rate, the highest influenza positive rate occurred in winter (December to February of the following year, 34.90%), followed by autumn (September to November, 20.92%) and spring (March to May, 18.11%). High variation was also observed in monthly positive rate, varying from zero to 62.38% (January 2019). The annual positive rate of influenza A was 13.32%. Stratifying by its subtypes, the positive rates of A/H1N1 and A/H3N2 were 5.73% and 7.60%, respectively. The annual positive rate of influenza B was 8.86%, with the positive rates of B/Yamagata and B/Victoria at 2.04% and 4.98%, respectively. More details were provided in Table 1 and Figs. 1, 2.

**Demographic characteristic differences among influenza virus types and subtypes/lineages**
During the study period, the influenza positive rate varied across age groups (p < 0.001), with the highest among 5–14 years old (36.33%), followed by 15–24 years old (24.42%), 25–59 years old (19.20%), ≥ 60 years old (15.12%), and children younger than 4 years old (11.39%).

For influenza A virus subtypes, the positive rates of A/H3N2 were much higher than those of A/H1N1 for most of the age groups except for the 25–59 years old group. For influenza B virus lineages, the positive rates of B/Victoria were much higher than those of B/Yamagata for most of the age groups except for people aged ≥ 60. More details were provided in Table 1. Overall, significant differences were observed in the positive rates of influenza virus subtypes/lineages among age groups but not between gender groups.
Table 1: Characteristics of influenza specimens in Chongqing, China, from 2010 to 2019

<table>
<thead>
<tr>
<th>characteristics</th>
<th>No. of influenza cases (%)</th>
<th>No. of influenza A (%)</th>
<th>No. of influenza B (%)</th>
<th>P-value</th>
<th>No. of influenza A (%)</th>
<th>P-value</th>
<th>No. of influenza B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>3,549</td>
<td>659 (18.57)</td>
<td>277 (7.81)</td>
<td></td>
<td>382 (10.76)</td>
<td>0.001</td>
<td>52 (1.46)</td>
</tr>
<tr>
<td>2011</td>
<td>3,237</td>
<td>366 (11.31)</td>
<td>184 (5.68)</td>
<td></td>
<td>182 (5.62)</td>
<td>0.557</td>
<td>158 (4.88)</td>
</tr>
<tr>
<td>2012</td>
<td>3,781</td>
<td>754 (19.94)</td>
<td>471 (12.46)</td>
<td></td>
<td>283 (7.48)</td>
<td>0.203</td>
<td>4 (0.11)</td>
</tr>
<tr>
<td>2013</td>
<td>5,962</td>
<td>752 (12.61)</td>
<td>595 (9.98)</td>
<td></td>
<td>154 (2.58)</td>
<td>0.053</td>
<td>504 (8.45)</td>
</tr>
<tr>
<td>2014</td>
<td>5,640</td>
<td>703 (12.46)</td>
<td>476 (8.44)</td>
<td></td>
<td>226 (4.01)</td>
<td>0.053</td>
<td>30 (0.53)</td>
</tr>
<tr>
<td>2015</td>
<td>6,221</td>
<td>739 (11.88)</td>
<td>453 (7.28)</td>
<td></td>
<td>285 (4.58)</td>
<td>0.053</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>2016</td>
<td>7,235</td>
<td>1,328 (18.36)</td>
<td>630 (8.71)</td>
<td></td>
<td>698 (9.65)</td>
<td>0.053</td>
<td>62 (0.86)</td>
</tr>
<tr>
<td>2017</td>
<td>9,040</td>
<td>2,522 (27.90)</td>
<td>1,225 (13.55)</td>
<td></td>
<td>1,293 (14.30)</td>
<td>0.053</td>
<td>659 (7.29)</td>
</tr>
<tr>
<td>2018</td>
<td>8,139</td>
<td>1,784 (21.92)</td>
<td>1,589 (19.52)</td>
<td></td>
<td>191 (2.45)</td>
<td>0.436</td>
<td>1,287 (15.81)</td>
</tr>
<tr>
<td>2019</td>
<td>10,822</td>
<td>4,529 (41.85)</td>
<td>2,578 (23.82)</td>
<td></td>
<td>1,945 (17.97)</td>
<td>0.034</td>
<td>888 (8.21)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34,878</td>
<td>7,670 (22.00)</td>
<td>4,624 (13.26)</td>
<td></td>
<td>3,038 (8.71)</td>
<td>0.436</td>
<td>1,976 (5.67)</td>
</tr>
<tr>
<td>Female</td>
<td>28,748</td>
<td>6,466 (22.50)</td>
<td>3,854 (11.05)</td>
<td></td>
<td>2,601 (9.05)</td>
<td>0.002</td>
<td>1,668 (5.80)</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>23,961</td>
<td>2,729 (11.39)</td>
<td>1,845 (7.53)</td>
<td></td>
<td>881 (3.68)</td>
<td>0.001</td>
<td>894 (3.73)</td>
</tr>
<tr>
<td>5–14</td>
<td>21,798</td>
<td>7,695 (36.33)</td>
<td>3,876 (18.30)</td>
<td></td>
<td>3,810 (17.99)</td>
<td>0.001</td>
<td>1,457 (6.88)</td>
</tr>
<tr>
<td>15–24</td>
<td>5,962</td>
<td>1,317 (24.42)</td>
<td>908 (16.83)</td>
<td></td>
<td>407 (7.55)</td>
<td>0.001</td>
<td>369 (6.83)</td>
</tr>
<tr>
<td>25–59</td>
<td>10,194</td>
<td>1,957 (19.20)</td>
<td>1,492 (14.64)</td>
<td></td>
<td>460 (4.51)</td>
<td>0.001</td>
<td>765 (7.50)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2,896</td>
<td>438 (15.12)</td>
<td>357 (12.33)</td>
<td></td>
<td>81 (2.80)</td>
<td>0.001</td>
<td>159 (5.50)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>16,967</td>
<td>3,073 (18.11)</td>
<td>1,036 (6.09)</td>
<td></td>
<td>2,016 (11.88)</td>
<td>0.001</td>
<td>738 (4.35)</td>
</tr>
<tr>
<td>Summer</td>
<td>13,950</td>
<td>1,743 (12.49)</td>
<td>1,371 (9.83)</td>
<td></td>
<td>370 (2.65)</td>
<td>0.001</td>
<td>43 (0.31)</td>
</tr>
<tr>
<td>Autumn</td>
<td>14,995</td>
<td>3,137 (20.92)</td>
<td>1,941 (12.94)</td>
<td></td>
<td>1,200 (8.00)</td>
<td>0.001</td>
<td>272 (1.81)</td>
</tr>
<tr>
<td>Winter</td>
<td>17,714</td>
<td>6,183 (34.90)</td>
<td>4,133 (23.33)</td>
<td></td>
<td>2,053 (11.59)</td>
<td>0.001</td>
<td>2,591 (14.63)</td>
</tr>
<tr>
<td>Total</td>
<td>63,626</td>
<td>14,136 (22.22)</td>
<td>8,478 (13.32)</td>
<td></td>
<td>5,639 (8.66)</td>
<td>0.001</td>
<td>3,644 (5.73)</td>
</tr>
</tbody>
</table>

*No: Number, co-infection: two or more virus identified was labeled as co-infection. [9]

Epidemic differences among influenza virus types and subtypes/lineages
Influenza A and influenza B positive rates varied significantly by year (p < 0.001). The highest influenza positive rate occurred in 2019 (41.85%), whereas the lowest rate occurred in 2011 (11.31%). A/H3N2, A/H1N1 and B/Victoria were predominant in 2012, 2018 and 2019. Significant difference of influenza virus subtypes/lineages was found among different years. More details were provided in Table 1.

Regarding seasonal patterns, influenza A had a higher positive rate than influenza B in summer, autumn and winter, except in spring. During the seasons of spring, summer, autumn, and winter, the influenza subtypes/lineages with the highest positive rates were B/Victoria (8.02%), A/H3N2 (9.52%), A/H3N2 (11.31%), and A/H1N1 (14.63%). Significant difference was observed in influenza virus subtypes/lineages by seasons. More details were provided in Table 1 and Fig. 2.

**Matching of trivalent vaccine strains and circulating strains of influenza B virus**

During 2013–2019, the prevalent strains of influenza B virus in Chongqing were matched with the B lineage contained in the trivalent influenza vaccine, except for 2018. The 2018 circulating strain was B/Yamagata whereas the vaccine strain was B/Colorado/06/2017. No data was obtained in the first three years, 2010–2012, because no influenza B specimen was typed. (Table 2).

<table>
<thead>
<tr>
<th>Year</th>
<th>Strain in the vaccine*</th>
<th>The circulating influenza virus strains</th>
<th>Match or Not</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>B/Brisbane/60/2008</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>B/Brisbane/60/2008</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2012</td>
<td>B/Wisconsin/1/2010</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2013</td>
<td>B/Massachusetts/2/2012</td>
<td>B/Yamagata</td>
<td>Yes</td>
</tr>
<tr>
<td>2014</td>
<td>B/Massachusetts/2/2012</td>
<td>B/Yamagata</td>
<td>Yes</td>
</tr>
<tr>
<td>2015</td>
<td>B/Phuket/3073/2013</td>
<td>B/Yamagata</td>
<td>Yes</td>
</tr>
<tr>
<td>2016</td>
<td>B/Brisbane/60/2008</td>
<td>B/Victoria</td>
<td>Yes</td>
</tr>
<tr>
<td>2017</td>
<td>B/Brisbane/60/2008</td>
<td>B/Victoria</td>
<td>Yes</td>
</tr>
<tr>
<td>2018</td>
<td>B/Colorado/06/2017</td>
<td>B/Yamagata</td>
<td>No</td>
</tr>
<tr>
<td>2019</td>
<td>B/Colorado/06/2017</td>
<td>B/Victoria</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Data sources: refer to the antigenicity analysis results of influenza weekly report of Chinese Center for Disease Control and Prevention; "-": no data

**Discussion**

In this study, we compared the relative contribution and epidemic patterns of the different influenza virus types and subtypes/lineages for 10 years in Chongqing, China. The study highlights the complexity of influenza in this area.

The result showed the different positive rates among different age groups (p = 0.001). During the study period, the overall influenza positivity rate (22.22%) was highest among children aged 5–14 years (36.33%), followed by those aged 15–24 years (24.42%), the lowest rate was found in children aged less than 5 years (11.39%), which was consistent with previous studies [10–13]. This phenomenon may be due to the fact that majority of children aged 5–14 years were students who attend school in densely populated classrooms with limited ventilation, have poor hygiene and disease prevention awareness, and are more susceptible to influenza transmission due to their young age and weak immunity, leading to a high incidence of influenza. Therefore, influenza prevention and control measures should be prioritized at the levels of schools and childcare institutions, with a focus on strengthening health education and implementing effective protective measures including targeted influenza vaccination campaigns [14–16].

The level of influenza activity continued to increase during 2010–2019, which has been reflected throughout the country [17–19]. The surge in 2019 can be primarily attributed to the revision of the Guidelines for diagnosis and treatment of influenza, which incorporated the utilization of a rapid antigen test as a diagnostic criterion [20].

Our results showed that influenza A dominated over influenza B during the study period, consistent with the studies in other cities in China [21–23]. From 2010 to 2019, B/Victoria and B/Yamagata alternated in dominance, showing a Z-shaped pattern [24]. B/Victoria was more dominant than B/Yamagata in 2016, 2017, and 2019, which was consistent with previous studies on various regions across the country [24–27]. Our results showed that influenza epidemics in Chongqing tend to occur in spring and winter but influenza B viruses were primarily dominant in the spring season [9, 10]. During this period, the public should pay attention to non-pharmaceutical prevention measures, such as washing hands, wearing masks, opening windows for ventilation frequently.

To prevent vaccine strain and circulating strain mismatch, the World Health Organization (WHO) proposed that seasonal influenza vaccines should include two B lineage strains in 2012. Beginning from the 2013–2014 influenza season in the northern hemisphere, the recommendation for the quadrivalent vaccine was initiated [28]. In 2018, China approved the use of the quadrivalent vaccine. Our study found that the prevalent B-type influenza strain matched well with the B lineage included in the influenza vaccine in most years, except for 2018, consistent with earlier studies [29–31]. Related research has indicated that despite a mismatch between the vaccine strains and the circulating strains of influenza B, there is still a discernible reduce in the burden of influenza B
disease to a certain extent [32, 33]. Therefore, comprehensive and multi-level promotion of influenza vaccination in Chongqing is still necessary to enhance population protection.

The study has limitations that warrant discussion. Influenza B lineage identification, which differentiated B/Yamagata and B/Victoria, was not performed in some specimens during 2010–2012. In addition, the impact of influenza vaccination coverage, environmental factors, and climate factors on influenza epidemics was not included in this study.

**Conclusion**

In summary, the study showed significant variations in epidemic patterns, including seasonal epidemic period and age distributions, among different influenza types, subtypes/lineages in Chongqing. Influenza A dominated over influenza B in most years, but influenza B was more likely to be prevalent during the spring, with alternating spring epidemics of influenza B/Victoria and influenza B/Yamagata. Matched influenza strains and vaccine strains was observed from 2013 to 2019, except for the year 2018. It is urgent to promote region-specific influenza vaccination policies and other preventive measures tailored to address the complicated dynamics of influenza in this area.

**Declarations**

**Data availability statement**

The data that support the findings of this study are available from the corresponding author, LQ, upon reasonable request.

**Funding source**

This study was supported by Chongqing Science and Technology Bureau (number: CSTC2021jscx-gksb-N0005)

**Ethical approval**

This study received appropriate approval from the ethics committee of the Chongqing Municipal Center for Disease Control and Prevention (Record number: 2021026).

**Author contributions statements**

XF, LQ, and JL contributed to the study concept and design; YX, JY, ZL, and SY contributed to data acquisition; XF, JL, XY and ZL contributed to data analysis; XF, JL, JY, SY and ZL contributed to the initial drafting of the manuscript, DT and LQ revised the manuscript. All authors contributed to the discussion, reviewed, and approved the final version of the manuscript.

**Conflict of interest statement**

All authors declared no competing interests.

**References**


Figures
Figure 1

Temporal trends of influenza virus activity by subtypes/lineages

Figure 2

Distribution of positive rates by subtypes/lineages of influenza viruses A and B in different matching of trivalent vaccine strains and circulating strains of influenza B virus