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Regional characteristics of influenza seasonality patterns in mainland China, 2005-2017: a statistical modeling study

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Running title: Flu activity and vaccination in China
Abstract

**Background** The seasonal and antigenic characteristics of influenza are crucial to help understanding influenza activity and inform vaccine recommendations.

**Methods** We employed a generalized linear model with harmonic terms to quantify the seasonal pattern of influenza in China during 2005-2017, including amplitude (circulatory intensity), semiannual periodicity (given two peaks a year), annual peak time, and epidemic duration. The antigenic differences were distinguished as antigenic similarity between 2009 and 2020. We categorized regions above 33° N, between 27° N and 33° N, and below 27° N as the north, central, and south regions, respectively.

**Results** We estimated that the amplitude in the north region (median: 0.019, 95% CI: 0.018-0.021) was significantly higher than that in the central (median: 0.011, 95% CI: 0.01-0.012, p < 0.001) and south region (median: 0.008, 95% CI: 0.007-0.008, p < 0.001) for A/H3N2. The A/H3N2 in the central region had a semiannual periodicity (median: 0.548, 95% CI: 0.517-0.577), while no semiannual pattern was found in other regions or subtypes/lineages. The antigenic similarity was low (below 50% in the 2009-10, 2014-15, 2016-18, and 2019-20 seasons) for A/H3N2.

**Conclusions** Our study depicted the seasonal pattern differences and antigenic differences of influenza in China, which provides information for vaccination strategies.
Introduction

Seasonal influenza is among the major causes of illness and death worldwide. As the most populous country, China is faced with a heavy burden (annual mean of 6.5 influenza-associated excess respiratory deaths per 100000 person-seasons [1] and annual average of 2.5 excess influenza-like illness (ILI) consultations per 1000 person-years [2]). In China, influenza vaccination usually starts in September [3], and it has not been included in the National Immunization Program [4]; only a few regions have piloted free influenza vaccination for school-age children and/or elderly individuals [5]. The vaccine uptake rate remains low (1.7% for the 40-59-year-old population and 3.8% for the population over 60 years) [6].

Influenza activity in many temperate countries aligns well with the vaccine manufacturing and administration cycle, while some countries (mainly in tropical zones) have influenza occurrence align with the vaccine manufacturing and administration cycle in the opposite hemisphere [7]. Regarding China, our previous study indicated that region-specific vaccination strategies would be optimal because the huge range of latitudes splits China into three influenza regions [8]. Several site-specific (cities or provinces) studies within China [9-11] also indicated that different seasonal patterns were detected for influenza types and across different age groups. The current autumn shot of influenza vaccine maybe unable to protect against the intensified influenza activity during the summer-autumn season in the midlatitude region in China. The WHO annually recommends influenza vaccine composition for the Northern and Southern Hemispheres in approximately February and September, respectively. The influenza vaccine used in China is in line with WHO recommendations for the Northern
Hemisphere, and it is probably best to use a vaccine recommended for the Southern Hemisphere to deal with the summer peak if the components are not changed substantially.

To comprehensively understand the seasonal characteristics as well as the vaccine recommendations and the corresponding antigenicity, we conducted this study to quantify the influenza seasonal pattern among three regions (i.e., north, central and south) [8] by subtype/lineage during 2005-2017, and we systematically collected information on influenza vaccine recommendations and changes in antigenicity. This would provide evidence for optimal vaccine strategy recommendations and better vaccine strain usage in China.

**Methods**

**Data sources**

The National Influenza Surveillance Network was established in 2000 to monitor the activity of, as well as antigenic and genetic changes in, seasonal influenza viruses in China [12]. This network includes 62 provincial- and prefecture-level Centers for Disease Control and Prevention (CDCs, referred to as network laboratories) and 193 sentinel hospitals situated in 31 provinces in 2005 [12]. During the 2009 H1N1 pandemic, the National Influenza Surveillance Network was expanded to 411 network laboratories and 556 sentinel hospitals [13].

Nasopharyngeal swabs collected from outpatients with ILI (body temperature ≥ 38 °C with either cough or sore throat) in sentinel hospitals were transferred to network laboratories to
determine the type and subtype/lineage using virus isolation and/or reverse transcription polymerase chain reaction (RT–PCR) [14].

In addition, the National Influenza Center (NIC) and provincial reference centers conducted antigenic surveillance using influenza virus isolated from network laboratories. The sera of ferrets immunized with the influenza vaccine strain was tested using a haemagglutination inhibition (HI) assay against isolated circulating strains and the vaccine strain. And plaque reduction neutralization test (PRNT) will be conducted alternatively for H3N2 viruses have RBCs agglutination problem [15]. The isolated strains are recognized as low reactors (or as having low antigenic similarity) if the HI titres are 8 times lower than those of the vaccine strain [14]. The results are regularly reported in the weekly influenza report [16].

From the above surveillance network, we retrieved the following data: 1) the weekly number of specimens tested and the weekly positive proportion of specimens by subtype/lineage from 2005-2017; and 2) the weekly proportion of antigenic similarity with egg-derived (or cell-derived) WHO-recommended vaccine strains by subtype/lineage during 2009-2020. Quality control of data was implemented according to the quality assessment protocol of the National Influenza Surveillance Network, and more details with regard to the data quality assessment are presented in the Supplementary Appendix.

Moreover, to evaluate the influenza vaccine component changes between the Southern and Northern Hemispheres, we collected WHO influenza vaccine recommendations from the

**Data analysis**

A previous study demonstrated that the seasonality of influenza A varied between three geographical regions: above 33° N, between 27° N and 33° N, and below 27° N [8]. In our study, we used the same geographic regions and hereafter called them the north, central, and south regions. We employed a generalized linear model (GLM) with harmonic terms [17] to quantify the seasonal pattern of influenza in the three regions. The GLM refers to the formula below:

\[
flu_i(t) = a_i + b_i \times \cos(2\pi t / 52.17) + c_i \times \sin(2\pi t / 52.17) + d_i \times \cos(4\pi t / 52.17) + e_i \times \sin(4\pi t / 52.17) + \varepsilon_i(t)
\]

where two paired trigonometric terms denote half-year and whole-year periodicity; \(i\) indicates location, age group, or sex; \(flu_i(t)\) is the standardized influenza activity (the square root of the division of the number of positive tests in the week by the total number of specimens tested in the year); \(t\) is a running index for a week; \(b_i\), \(c_i\), \(d_i\), and \(e_i\) are seasonality coefficients and \(a_i\) is the intercept; and \(\varepsilon_i(t)\) is the error.

We then quantified the seasonality using metrics including amplitude, annual peak time, semiannual periodicity, and epidemic duration [17]. The amplitude indicated the circulatory
intensity, which was calculated as the square root of the summation of $b^2$ and $c^2$ (or $d^2$ and $e^2$). Higher amplitude revealed higher intensity of influenza activity. The annual peak time referred to the week when the activity intensified, which was estimated using $-\arctan(c/b)$. The semiannual periodicity was the ratio of the semiannual amplitude ($\sqrt{d^2 + e^2}$) to the summation of the annual ($\sqrt{b^2 + c^2}$) and semiannual amplitudes, which indicated the relative contribution of semiannual amplitude. A ratio close to 1 is indicative of dominant semi-annual periodicity while a ratio close to 0 indicates dominant annual periodicity, hence apparent semiannual circulation was defined as that the ratio was over 0.5 [8]. The epidemic duration was defined as the number of weeks above the average influenza activity (weekly average of $flu_i(t)$ estimated). Details of the derivation refers to Naumova et al. [17] and section 1 in the supplementary materials.

We compared the aforementioned metrics among the three regions to distinguish the spatial differences in influenza activity. We further explored age and sex differences. Additionally, we explored the change in influenza activity and seasonality before (2005-2009), during, and after the 2009 H1N1 pandemic (2010-2017). The Kruskal–Wallis rank sum test was conducted to determine statistical significance, and descriptive statistics are displayed as medians with 95% nonparametric bias-corrected accelerated bootstrap confidence intervals (BCa-CI, 95% CI for short hereafter). Multiple comparisons were conducted using Bonferroni adjustment, which was implemented through dividing the significance level by the number of tests [18,19].
A chi-square test was used to evaluate the antigenic similarity of egg-propagated and cell culture-propagated reference influenza viruses compared with circulating viruses. The antigenic similarity of local circulating viruses with the vaccine-recommended strains during the corresponding year and the year after was compared using McNemar’s test.

All statistical inferences were conducted based on a significance level of 0.05, adjusted p-values were reported for multiple comparisons and all analyses were performed using R (version 4.1.1).

Results

Seasonality after the 2009 pandemic

The seasonality varied among the three regions after the 2009 H1N1 pandemic (Figure 1). The amplitude of influenza A was higher than that of B, and most of the influenza cases showed a higher amplitude in the north region (Figure 1, Panel A). For instance, we found no significant difference in amplitude among the three regions for A/H1N1 (median: 0.012, 0.012, and 0.011 for the north, central, and south regions, respectively). For A/H3N2, the amplitude in the north region (median: 0.019, 95% CI: 0.018-0.021) was higher than that in the central (median: 0.011, 95% CI: 0.01-0.012, p < 0.001) and south regions (median: 0.008, 95% CI: 0.007-0.008, p < 0.001). No difference was found for B/Victoria (median: 0.006 for the north, central, and south regions), and B/Yamagata had the highest amplitude in the central region (median: 0.007, 95% CI: 0.007-0.008).
The annual influenza activity mostly peaked in the winter-spring season (1.8-13.9 weeks) for the A/H1N1 and influenza B lineages, while the annual peak occurred in the autumn season for A/H3N2 in the central region (median: 40.1, 95% CI: 39.1-41.6 weeks) and the summer season in the south region (median: 28.6, 95% CI: 25.8-33.2, Figure 1, Panel D). Moreover, we found that A/H3N2 in the central region had a semiannual periodicity (median: 0.548, 95% CI: 0.517-0.577), while no semiannual circulating pattern was found in other regions or for other subtypes/lineages (Figure 1, Panel B). Except for A/H3N2 (the central region had the longest duration), we found that the epidemic duration for other influenza subtypes/lineages decreased from the south to the central to the north region (Figure 1, Panel C).

The amplitude was much higher among people above 18 years of age for influenza A and higher among people below 17 years of age for influenza B (Figure 2, Table S1). Specifically, people aged 18-59 years showed the highest amplitude for A/H1N1, people aged over 60 years showed the highest amplitude for A/H3N2, and those aged 0-17 years showed the highest amplitude for B/Victoria and B/Yamagata (Figure 2). The influenza activity peaked in the winter-spring season for most age groups and flu subtypes/lineages, except for A/H3N2 in the central and south regions, which peaked in the summer-autumn season (Table S1). Even if the semiannual periodicity had a statistically significant difference among age groups, only values in the central region for A/H3N2 were above 0.5 (Table S1). The epidemic duration had a similar pattern as the regional difference, and no age disparity was found (Table S1). Moreover, we recognized no apparent sex disparity for influenza activity in subtype/lineage among the three regions (Table S2).

The amplitude in the central and south regions showed no statistical significance in the comparison before and after the pandemic for all influenza subtypes/lineages, while the amplitude in the north region showed a decreasing pattern from before, during, and after the 2009 H1N1 pandemic (Figure 3, Panels A-D). For influenza A, the peak time significantly gradually decreased from before to during and to after the pandemic, while the annual peak time gradually increased for influenza B (Figure 3, Panels E-H). Before the 2009 H1N1 pandemic, we found a significant semiannual cycle pattern of A/H3N2 in the central region (median: 0.584, 95% CI: 0.464-0.693), while the pattern disappeared (median: 0.431, 95% CI: 0.41-0.443) during the 2009 pandemic (Table S3). The semiannual periodicity resumed after the 2009 pandemic (median: 0.548, 95% CI: 0.517-0.577).

Changes in antigenicity

The antigenic data revealed that the vaccine recommended by the WHO was relatively similar to circulating strains in China for A/H1N1, B/Yamagata, and B/Victoria in most years (Table 1). The antigenic similarity was relatively low (below 50% in 2009-10, 2014-15, 2016-18, and 2019-20) for A/H3N2. Compared to the circulating strains, the antigenicity of cell-derived vaccine strains showed statistically higher similarities than the egg-derived strains (Table 2). The antigenicity of H3N2 between the according year and the year after showed no significant differences (Table S4).
Discussion

Following the three epidemiological regions characterized in our previous work [8], we further highlight that the semiannual epidemic cycle in the central region is consistent with A/H3N2 circulation after the 2009 H1N1 pandemic. The semiannual periodicity of A/H3N2 was also confirmed in studies conducted in some midlatitude cities in China [9,10]. Moreover, a significantly longer epidemic duration is estimated for A/H3N2 in the central region than in other regions, as the semiannual A/H3N2 cycle in the central region. However, the circulation patterns in the central and south regions vary greatly, shown as their wider confidence intervals. This indicates that the seasonality of influenza is more complicated in subregional geographical scale in the central and south regions.

A study conducted in Chengdu [20], a midlatitude city in southwestern China, found that the significant semiannual periodicity occasionally disappeared during 2011-2014. Local meteorological factors, population mobility [21], and vaccination coverage could shape this unique seasonality. The semiannual circulating pattern of influenza is important to consider when planning routine influenza immunization campaigns in China, as they entail different vaccination timings.

Regarding seasonality among different age groups and sexes, we found that the influenza A subtype activity was higher among older adults, whereas higher activity for the influenza B lineage was found among children. A study [11,20] conducted in Yichang City, which is located in the subtropical region of China, also indicated a higher positive rate among children aged 5-
14 years as well as among individuals over 60 years old. Another research [20] found that the influenza positive rate shifts from school-aged children to adults and the elderly for A/H1N1 and A/H3N2, while the distribution varies by subtype/lineage and by season. The higher activity may reveal a relatively higher susceptibility among those specific ages, and it is consistent with studies on the disease burden of influenza [1,2,12,13]. The seasonal pattern was not significantly different by sex in our analyses. This finding matches the study on all-cause excess mortality associated with influenza in Shanghai, 2010-2015 [22]. The age distribution of influenza activity as well as its burden is crucial for determining the target population or priority for vaccination, which could help policymakers to support free vaccination programs for populations with a higher risk.

In addition to the timing and target population of vaccination programs, the matching level between recommended vaccine components and circulating virus strains plays an important role in vaccine function. To distinguish the antigenic similarity, the HI assay is commonly conducted, while some A/H3N2 viruses have red blood cell (RBC) agglutination problems. Hence, for those A/H3N2 viruses with agglutination problems, neutralization assays are often used instead to support the antigenic data [15,23]. However, the HI titers correlate well with those detected by more complicated virus neutralizing assays [24-26]; that is, the antigenic similarity should be the same through HI and neutralizing assays if no agglutination problem exists. Consequently, the antigenic data summarized from the NIC influenza weekly report can compatibly reveal the matching level between the recommended vaccine components and circulating virus strains. We found that the mismatch for A/H3N2 occurred the most frequently (2009-10, 2014-15, 2016-18, and 2019-20). A frequent mismatch for A/H3N2 has also been
noted by several studies through a genetic approach [27,28]. However, better antigenic similarity for cell-derived vaccine strains in A/H3N2 is observed compared to egg-derived strains (see Table 2). As a different strategy, cell-derived/recombinant HA can avoid potential egg adaptation mutations in HA [29], providing flexibility in production [30]. Additionally, a vaccine efficacy trial revealed that nonegg-derived influenza vaccines are better than egg-derived vaccines [31,32]. However, more real-world vaccine efficacy/effectiveness studies are still needed in more populations and regions to verify their superiority in the real-world.

In 2009, a novel H1N1 virus caused a pandemic. The circulation of influenza A was of equal or higher intensity than that before the pandemic, while little influence can be seen for influenza B. Our model indicates that the circulatory intensity (amplitude) in the north region was reduced while remaining similar to the pre-pandemic level in the central and south regions. The peak time for influenza A has been delayed since the pandemic, which is especially apparent for A/H1N1. The changing influenza seasonality may mainly be due to the emergency of the novel A/H1N1 virus, which completely replaced the former seasonal H1N1 after the 2009 pandemic. On the other hand, several studies indicate that the human behavior was inevitably changed [33,34], which could also contribute to the changing seasonality. The changing seasonality and its contributors are key for routine influenza immunization campaign recommendations.

The current influenza vaccination program in China starts in September, using the WHO recommended composition of influenza virus vaccines in the Northern hemisphere. The
guidelines recommend high-risk populations including elderly individuals over 60 years old and children aged six months to 5 years old, to get vaccinated as a priority [3]. In China, inactivated influenza vaccine (IIV, includes both trivalent and quadrivalent), live attenuated influenza vaccine (LAIV, only trivalent), and subunit vaccines (only trivalent) are available, and since 2019, the National Institutes for Food and Drug Control has issued a quadrivalent influenza vaccine (QIV).

In practice, all regions in China can only supply influenza vaccines before the winter epidemic (approximately before January). For the central region, A/H3N2 shows apparent semiannual periodicity through our analyses. It would be valuable to add an additional dose of influenza vaccination before the summer A/H3N2 peak (before late May), given the 6-8 month duration of vaccine-induced protection [35]. However, this introduces problems for manufacturing and implementation. In 2015, the Chinese Hong Kong government purchased influenza vaccines formulated for the Southern hemisphere to vaccinate elderly individuals prior to the summer peak of influenza [36]. This was the first time that an area in the Northern hemisphere used an influenza vaccine with a formulation recommended for the opposite hemisphere. A subsequent serological study of people who received the additional dose of influenza vaccine indicated better humoral immunity than those who did not [37]. Reviewing the WHO influenza vaccine recommendation, we found no significant difference in antigenic similarity when comparing vaccine strains used in the corresponding year with vaccine strains recommended later. This indicates the potential necessity and possibility of implementing additional vaccination campaigns in the central region.
Our findings of higher circulation of influenza among children (below 18) as well as the elderly (above 60) well matches the recommended priorities according to the guidelines [3]. Children are more influenced by influenza B (higher amplitude), while QIV is available for individuals over 3 years of age, not for children aged 6-35 months in China, which has been approved for people 6 months of age and older in the US. Moreover, several studies [38,39] have indicated that QIV may provide better protection for children than TIV. Regarding the high activity of influenza B among children, we recommend facilitating the expansion of age for QIV and promoting a free influenza vaccine policy for school children [39] to improve coverage.

To provide long-lasting and universal immunity against influenza virus, much effort has been put into developing new influenza vaccines to prevent problems caused by antigenic shift/drift. Cell-based vaccines have been developed to avoid the egg-adaption problem as well as to improve productivity [30]. Several different influenza vaccine routes have been developed (preclinical or in different phases of trials), including mRNA [40], and plant-derived [41], etc. Regarding the higher antigenic similarity observed for egg-derived vaccine strains through national influenza surveillance, we recommend more studies on the vaccine efficacy/effectiveness of new influenza vaccines and to promote their usage.

However, influenza vaccine uptake is still low in China. Through the influenza vaccine lot information (see Supplementary Materials Section 6, Figure S2), the yearly vaccine lot has increased substantially in recent years. More than 50% of vaccine lots were quadrivalent
influenza vaccines (QIVs). However, the total volume (approximately 58 million doses) is still insufficient considering real-world vaccine uptake. The policy of free or financial aid influenza vaccination programs implemented in some regions can significantly improve the vaccine coverage [42].

Our work has several limitations. First, our data were limited to the 2016-2017 season due to the unavailability of detailed influenza surveillance data after that year. The timely analysis of the latest influenza activity, especially the period after the coronavirus disease 2019 (COVID-19) pandemic, will help understand the changing pattern of influenza seasonality with intense nonpharmaceutical interventions (NPIs) as well as changing human behaviors. A study conducted by Feng et al. [43] indicated significant suppression of influenza activity in early 2020. Moreover, a systematic review [44] indicated a reduction in influenza burden caused by NPIs implemented during the 2019-2020 season. Second, the changes in the influenza surveillance system could impact the positive rate, which is the key measure representing the influenza activity. The influenza surveillance system in China has been expanded since the 2009 H1N1 pandemic [2], and sentinel hospitals were routinely supervised and changed if they were not qualified. Possible bias associated with differences in specimen sampling and laboratory methods over time clearly influences the positive rate. Hence, we standardized the positive rate [8] by the year total specimens tested, which can reduce possible bias. Third, to give a quantified estimation for influenza seasonality changes, we employed a GLM with harmonic terms. This model framework successfully estimated the average pattern, but it may have obscured the two-year seasonality (mostly occurring in the influenza B lineage [45]). Finally, the antigenic comparisons between egg- and cell-derived vaccine strains have been
limited in recent years. Therefore, monitoring the antigenic difference between egg- and cell-based strains is necessary, and more real-world evidence for egg- and cell-derived influenza vaccines is needed.

In conclusion, our analysis of historical data on influenza activity and antigenic characteristics provides information to support the development of optimal vaccination strategies for different regions and age groups in China. We uncovered the important contribution of A/H3N2 to the semiannual cycle pattern in the central region and the summer peak in the south region. Prolonging the influenza vaccination campaign or introducing a vaccination before summer in some regions can be taken into consideration to reduce the burden of influenza. Antigenic mismatch occurs most often in A/H3N2, and the cell-derived vaccine was found to be superior to the egg-derived vaccine in terms of antigenicity. To provide better protection and production flexibility, we suggest expanding the use of cell-derived, recombinant influenza vaccines with more exploration of their real-world effectiveness. The age disparity in seasonality is already covered by the high-risk populations recommended to receive influenza vaccination, while the influence on transmission along with vaccination remains to be determined. While the long-lasting global pandemic of COVID-19 could disrupt the seasonality of influenza, continuous analyses of seasonality after 2020 are needed.

**Declaration of competing Interests**
HY received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company, and SINOVAC Biotech Ltd. All the other authors have no competing interests.

Author Contributions

HY conceived the study. XD, ZC, and ZZ collected data. XD and ZC analyzed the data. XD, ZC and JY wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and edited the manuscript.

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Ethical Approval statement

This study is a modeling study using data on aggregated data of influenza activity and antigenicity in China. The data provided for analysis of this study did not contain patients’ identification. Therefore, this study did not require ethical approval.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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**Figure 1.** Seasonality among the north, central, and south by subtype/lineage after the 2009 H1N1 pandemic (2010-2017). A) The amplitude: influenza A is more active than B, and only A/H3N2 and B/Yamagata show region difference. B) Semi-annual cycle pattern: Only A/H3N2 in the central had significant semi-annual periodicity (above 0.5, the dashed reference line). C) Epidemic duration: The relative epidemic duration for influenza A and B ranged from 17 to 34 weeks. D) Annual peaking time: A/H1N1, A/H3N2 (in the North) and influenza B lineage yearly peaked at winter-spring season, while A/H3N2 in the central and south peaked at summer-autumn season.
Figure 2. Seasonality (the amplitude) among 0-17, 18-59, and 60+ by subtype/lineage in three regions after the 2009 H1N1 pandemic (2010-2017). People aged 18-59 had the highest amplitude for A/H1N1, people aged over 60 had the highest amplitude for A/H3N2, and people aged 0-17 years had the highest amplitude for influenza B lineage.
Figure 3. Seasonality among the north, central, and south by subtype/lineage before (2005-2009), during and after the 2009 H1N1 pandemic (2010-2017). A/H1N1, A/H3N2, B/Victoria, and B/Yamagata from the 1st column on the left to the 4th column on the right. **The amplitude:** Only the amplitude in north region showed decreased pattern from before, to during, and to after the 2009 H1N1 pandemic. **Annual peaking time:** As for influenza A, the peaking time gradually delayed from before, to during, and to after the 2009 pandemic with statistical significance, while the annual peaking time gradually advanced for influenza B.
Table 1. Antigenic similarity for influenza from 2009-2020 by subtype/lineage.

<table>
<thead>
<tr>
<th>Flu season</th>
<th>A/H1N1</th>
<th>A/H3N2</th>
<th>B/Victoria</th>
<th>B/Yamagata</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2010</td>
<td>96.9 (1632/1685)</td>
<td>36.6 (371/1013)</td>
<td>59.4 (2772/4666)</td>
<td>67.7 (400/591)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>95.8 (1315/1373)</td>
<td>96.7 (1657/1714)</td>
<td>92.5 (825/892)</td>
<td>49.8 (401/805)</td>
</tr>
<tr>
<td>2011-2012</td>
<td>87 (40/46)</td>
<td>77.5 (2153/2778)</td>
<td>72.6 (2052/2828)</td>
<td>90 (1533/1704)</td>
</tr>
<tr>
<td>2012-2013</td>
<td>99.6 (532/534)</td>
<td>88.5 (850/960)</td>
<td>94.6 (157/166)</td>
<td>100 (144/144)</td>
</tr>
<tr>
<td>2013-2014</td>
<td>99.8 (1307/1309)</td>
<td>99.5 (1535/1542)</td>
<td>67.5 (52/77)</td>
<td>94.7 (1407/1485)</td>
</tr>
<tr>
<td>2014-2015</td>
<td>97.2 (69/71)</td>
<td>28.3 (478/1692)</td>
<td>42.5 (31/73)</td>
<td>91.2 (1195/1311)</td>
</tr>
<tr>
<td>2015-2016</td>
<td>96.9 (693/715)</td>
<td>56 (183/327)</td>
<td>78.6 (827/1052)</td>
<td>98.6 (580/588)</td>
</tr>
<tr>
<td>2016-2017</td>
<td>96 (3098/3227)</td>
<td>41.6 (412/990)</td>
<td>83.3 (883/1060)</td>
<td>95.6 (451/472)</td>
</tr>
<tr>
<td>2017-2018</td>
<td>92.8 (784/845)</td>
<td>34.7 (134/386)</td>
<td>60.4 (154/255)</td>
<td>97.5 (847/869)</td>
</tr>
<tr>
<td>2018-2019</td>
<td>97.7 (2000/2047)</td>
<td>78.5 (729/929)</td>
<td>43.4 (626/1444)</td>
<td>98.3 (58/59)</td>
</tr>
<tr>
<td>2019-2020</td>
<td>96.6 (802/830)</td>
<td>3.7 (44/1175)</td>
<td>16.9 (182/1077)</td>
<td>100 (2/2)</td>
</tr>
</tbody>
</table>
**Table 2.** Antigenic similarity for cell-derived and egg-derived A/H3N2 vaccine strains from 2015-2020

<table>
<thead>
<tr>
<th>Flu season</th>
<th>Cell-derived</th>
<th></th>
<th>Egg-derived</th>
<th></th>
<th>P-value</th>
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